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(71) Applicant (*for all designated States except US*): **ASTRAZENECA AB** [SE/SE]; Södertalje, S-SE-151 85 (SE).

(71) Applicant (*for MG only*): **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BONNERT, Roger, Victor** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **PATEL, Anil** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **THOM, Stephen** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-SE-151 85 Södertalje (SE).

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(54) Title: NOVEL COMPOUNDS

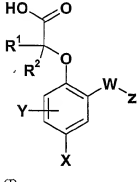
(57) Abstract: The invention relates to substituted phenoxyacetic acids as useful pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

NOVEL COMPOUNDS

The present invention relates to substituted phenoxyacetic acids as useful pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

EPA 1 170 594 discloses methods for the identification of compounds useful for the treatment of disease states mediated by prostaglandin D2, a ligand for orphan receptor CRTH2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. It has been found that certain phenoxyacetic acids are active at the CRTH2 receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

In a first aspect the invention therefore provides a method of treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial, which comprises administering to a patient a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

in which:

W is O, $S(O)_n$ (where n is 0, 1 or 2), NR^{15}, CR^1OR^2 or CR^1R^2

X is hydrogen, halogen, cyano, nitro, $S(O)_n R^6$, OR^{12} or C_{1-6}alkyl which may be substituted by one or more halogen atoms;

Y is selected from hydrogen, halogen, CN, nitro, SO_2R^3, OR^4, SR^4, SOR^3, $SO_2NR^4R^5$, $CONR^4R^5$, NR^4R^5, $NR^6SO_2R^3$, $NR^6CO_2R^6$, NR^6COR^3, C_2-C_6 alkenyl, C_2-C_6 alkynyl,

C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, OR^6 and NR^6R^7, $S(O)_nR^6$ where n is 0, 1 or 2;

Z is aryl or heteroaryl, optionally substituted by one or more substituents independently selected from from hydrogen, halogen, CN, OH, SH, nitro, CO_2R^6, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NR^6CO_2R^6$, $NHCOR^9$, NR^9COR^9, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6, NR^6R^7, $S(O)_nR^6$ (where n is 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$.

R^1 and R^2 independently represent a hydrogen atom, halogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or a C_{1-6}alkyl group, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, NR^6R^7, OR^6, $S(O)_nR^6$ (where n is 0, 1 or 2);

or

R^1 and R^2 together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^6 and itself optionally substituted by one or more C_1-C_3 alkyl or halogen;

R^3 represents C_3-C_7 cycloalkyl or C_{1-6}alkyl either of which may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0,1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^4 and R^5 independently represent hydrogen, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0,1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

or

R^4 and R^5 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_n$ (where n = 0,1 or 2), NR^8, and itself optionally substituted by halogen or C_{1-3} alkyl;

R^6 and R^7 independently represents a hydrogen atom or C_1-C_6 alkyl;

R^8 is hydrogen, C_{1-4} alkyl, -COC_1-C_4 alkyl, CO_2C_1-C_4alkyl, SO_2R^6 or $CONR^6C_1$-C_4alkyl;

R^9 represents aryl, heteroaryl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, aryl, heteroaryl OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^{10} and R^{11} independently represent aryl or heteroaryl, hydrogen, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, aryl, heteroaryl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_n$ (where n = 0, 1 or 2), NR^8, and itself optionally substituted by halogen or C_1-C_3 alkyl,

R^{12} represents a hydrogen atom or C_{1-6}alkyl which may be substituted by one or more halogen atoms, and

R^{15} represents a hydrogen atom, C_1-C_6 alkyl, SO_2R^6 or COR^6.

Examples of aryl include phenyl and naphthyl.

Heteroaryl is defined as a 5-7 membered aromatic ring or can be a 6,6- or 6,5-fused bicyclic ring, all optionally containing one or more heteroatoms selected from N, S and O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene, naphthyl, indene, quinoline, isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole, benzimidazole, benzthiazole, benzoxazole, purine, 4H-quinolizine, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine and quinolone.

Aryl or heteroaryl groups can be optionally substituted by one or more substituents independently selected from hydrogen, halogen, CN, OH, SH, nitro, CO_2R^6, SO_2R^9, OR^9,

SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NR^6CO_2R^6$, $NHCOR^9$, NR^9COR^9, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6, NR^6R^7, $S(O)_nR^6$ (where n is 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$. Substituents can be present at any suitable position on the aryl and heteroaryl rings, including nitrogen atoms where appropriate.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched.

Heterocyclic rings as defined for R^4, R^5 and R^{10} and R^{11} means saturated heterocycles, examples include morpholine, azetidine, pyrrolidine, piperidine and piperazine.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

Preferably W is O, $S(O)_n$ (where n is 0, 1 or 2), CR^1R^2 or NR^{15} where R^{15} is hydrogen or methyl.

More preferably W is O, CH_2 or NR^{15} where R^{15} is hydrogen or methyl.

Even more preferably W is O, CH_2 or NH.

Most preferably W is O.

Preferably X is halogen, in particular fluoro and chloro, or C_{1-2}alkyl optionally substituted with one or more halogen atoms, such as CF_3.

More preferably X is fluoro, chloro or trifluoromethyl.

Even more preferably X is fluoro or chloro.

Preferably Y is hydrogen, halogen, in particular fluoro and chloro or C_{1-6}alkyl, such as methyl.

More preferably Y is hydrogen or halogen, in particular fluoro and chloro.

Even more preferably Y is hydrogen.

Preferably Z is phenyl, pyridyl or pyrimidyl, optionally substituted as defined above, more preferably Z is phenyl optionally substituted as defined above.

Preferred substituents for all Z groups include those substituents exemplified herein, in particular halogen, CN, C_{1-3}alkyl optionally substituted with one or more halogen atoms, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NHCOR^9$ or NR^9COR^9. Preferably R^9 is methyl or ethyl.

More preferred substituents for all Z groups include halogen, in particular fluoro and chloro, C_{1-3}alkyl optionally substituted with one or more halogen atoms, SO_2R^9, $SO_2NR^{10}R^{11}$, $NHSO_2R^9$ or $NR^9SO_2R^9$.

Preferably Z is phenyl substituted by one or two substituents, preferably the substituent in the 4-position is selected from SO_2R^9, $SO_2NR^{10}R^{11}$, $NHSO_2R^9$ or $NR^9SO_2R^9$. Preferably R^9 is methyl or ethyl. Preferably R^{10} and R^{11} are both methyl.

Preferably Z is phenyl substituted by two substituents, preferably the substituent in the 4-position is selected from SO_2R^9, SO_2NMe_2, $NHSO_2R^9$ or $NR^9SO_2R^9$ where R^9 is methyl or ethyl and the sustituent in the 2- or 3-position is selected from fluoro, chloro or C_{1-3}alkyl optionally substituted with one or more halogen atoms.

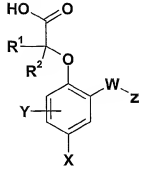
Preferably R^1 and R^2 are independently hydrogen or C_{1-3} alkyl.

More preferably R^1 and R^2 are independently hydrogen or methyl.

Preferably when R^1 is alkyl and R^2 is hydrogen in the acid chain, the S-isomer is preferred

Preferred compounds of formula (I) include those compounds exemplified herein, both in free base form as well as pharmaceutically acceptable salts and solvates thereof.

In a further aspect the invention provides a sub-set of compounds of formula (I), i.e. compounds of formula (IA) or pharmaceutically acceptable salts or solvates thereof:



(IA)

in which:

W is O, CH_2, $S(O)_n$ (where n is 0, 1 or 2) or NR^{15} where R^{15} is hydrogen or methyl;

X is halogen or C_{1-6}alkyl which may be substituted by one or more halogen atoms;

Y is hydrogen, halogen or C_{1-6}alkyl;

Z is phenyl, pyridyl or pyrimidyl each optionally substituted by one or more substituents independently selected from from halogen, CN, C_{1-3}alkyl optionally substituted with one or more halogen atoms, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NHCOR^9$, NR^9COR^9;

R^1 and R^2 independently represent hydrogen or C_{1-6}alkyl;

R^6 and R^7 independently represent hydrogen atom or C_{1-6}alkyl;

R^8 is hydrogen, C_{1-4} alkyl, -COC_1-C_4 alkyl, CO_2C_1-C_4alkyl, SO_2R^6 or $CONR^6C_1$-C_4alkyl;

R^9 is C_{1-6}alkyl optionally substituted by halogen, and

R^{10} and R^{11} independently represent hydrogen or C_{1-6}alkyl,

provided that:

- the compounds 2-[4-methyl-2-(benzyl)phenoxy]acetic acid, 2-[4-chloro-2-(benzyl)phenoxy]propanopic acid, 2-[4-bromo-2-(4-chlorophenoxy)phenoxy]propanopic acid and 2-[4-chloro-2-(4-chlorophenoxy)phenoxy]propanopic acid are excluded;
- when X is fluoro and W is S, then Z is not 5-fluoro-2-hydroxyphenyl,

- when X is chloro, Y is 3-methyl, R^1 and R^2 are both hydrogen and W is CH_2, then Z is not phenyl.

Suitably W is O, CH_2, $S(O)_n$ (where n is 0, 1 or 2) or NR^{15} where R^{15} is hydrogen or methyl. Preferably W is O, S, CH_2, NH or NMe, more preferably W is O, CH_2 or NH, even more preferably W is O or NH, most preferably W is O.

Preferably R^1 and R^2 are independently hydrogen or methyl. More preferably R^1 and R^2 are both hydrogen or one is hydrogen and the other is methyl.

Preferably X is halogen, in particular fluoro and chloro, or C_{1-2}alkyl optionally substituted with one or more halogen atoms, such as CF_3.

More preferably X is fluoro, chloro or trifluoromethyl.

Even more preferably X is fluoro or chloro.

Preferably Y is hydrogen, halogen, in particular fluoro and chloro or C_{1-6}alkyl, such as methyl.

More preferably Y is hydrogen or halogen, in particular fluoro and chloro.

Even more preferably Y is hydrogen.

Preferably Z is phenyl substituted by two substituents, preferably the substituent in the 4-position is selected from SO_2R^9, $SO_2NR^{10}R^{11}$, $NHSO_2R^9$ or $NR^9SO_2R^9$ and the sustituent in the 2- or 3-position is selected from fluoro, chloro or C_{1-3}alkyl optionally substituted with one or more halogen atoms. Preferably R^9 is methyl or ethyl. Preferably R^{10} and R^{11} are both methyl.

Preferred compounds of formula (IA) include:
[4-Chloro-2-[[4-(ethylsulfonyl)phenyl]thio]phenoxy]- acetic acid,
[4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]phenoxy]- acetic acid,
[4-Chloro-2-[4-(ethylsulfonyl)phenoxy]phenoxy]- acetic acid,
[4-Chloro-2-[[4-(methylsulfonyl)phenyl]amino]phenoxy]- acetic acid,
(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
{4-Chloro-2-[(5-chloropyridin-2-yl)thio]phenoxy}acetic acid,

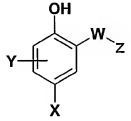
{4-Chloro-2-[(2-chloro-4-cyanophenyl)thio]phenoxy}acetic acid,
(4-Chloro-2-{[2-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfinyl}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfonyl}phenoxy)acetic acid,
[4-Chloro-2-({4-[(methylamino)carbonyl]phenyl}thio)phenoxy]acetic acid,
(2S)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2R)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)-2-methylpropanoic acid,
{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}acetic acid,
(2S)-2-{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid,
(2S)-2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid,
(2S)-2-{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}propanoic acid,
{4,5-Dichloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4,5-difluorophenoxy}acetic acid,
2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}-2-methylpropanoic acid,
(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)acetic acid,
(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)acetic acid,
[2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid,
(2S)-2-[2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]propanoic acid,
[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid,
(2S)-2-[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]propanoic acid,
[2-({4-[(Dimethylamino)sulfonyl]phenyl}thio)-4-(trifluoromethyl)phenoxy]acetic acid,
[2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid,
[2-[2-Chloro-4-(ethylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid,
2-[2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]butanoic acid,
[2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]acetic acid,
(2S)-2-[2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]propanoic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid,
{2-[2-Chloro-4-(ethylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid,
2-{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}-2-methylpropanoic acid,
(2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid,

(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid,
2-(2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)-2-methylpropanoic acid,
(2-{2-Chloro-4-[(ethylsulfonyl)amino]phenoxy}-4-fluorophenoxy)acetic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)propanoic acid,
2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)-2-methylpropanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)propanoic acid,
2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)-2-methylpropanoic acid,
[4-Chloro-2-(pyrimidin-5-yloxy)phenoxy]acetic acid,
[4-Chloro-2-(quinolin-3-yloxy)phenoxy]acetic acid,
(2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid,
(2S)-2-(2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)propanoic acid,
{4-Chloro-2-[[2-chloro-4-(methylsulfonyl)phenyl](methyl)amino]phenoxy}acetic acid,
{4-Chloro-2-[[2-chloro-4-(methylsulfonyl)phenyl](ethyl)amino]phenoxy}acetic acid,
(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]phenoxy}acetic acid,
[4-Chloro-2-(quinolin-8-ylthio)phenoxy]acetic acid,
(2*S*)-2-[4-Chloro-2-(4-nitrophenoxy)phenoxy]-propanoic acid,
(2S)-2-(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)propanoic acid,
2-(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)-2-methylpropanoic acid,
[2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid,
[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid
[2-[4-(Ethylsulfonyl)benzyl]-4-(trifluoromethyl)phenoxy]acetic acid,
[4-Chloro-2-(3-cyanobenzyl)phenoxy]acetic acid,
and pharmaceutically acceptable salts and solvates thereof.

The compound of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, tert-butylamine, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1999).

Compounds of formula (I) can be prepared by reaction of a compound of formula (II):



(II)

in which W, X, Y and Z are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (III):

$L\text{-}CR^1R^2CO_2R^{13}$ (III)

Where R^1 and R^2 are as defined in formula (I) or are protected derivatives thereof, R^{13} is H or C_1-C_{10} alkyl group and L is a leaving group, and optionally thereafter in any order:

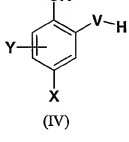
- removing any protecting group
- hydrolysing the ester group R^{13} to the corresponding acid
- oxidation of sulphides to sulphoxides or sulphones
- forming a pharmaceutically acceptable salt.

The reaction can be carried out in a suitable solvent such as DMF using a base such as potassium carbonate or the like. Suitable groups R^{13} include $C_{1\text{-}6}$ alkyl groups such as methyl, ethyl or tert-butyl. Suitable L is a leaving group such as halo, in particular chlorine or bromine. L may also be hydroxy so that a Mitsunobu reaction may be performed with compound (II) using for example triphenylphosphine and diethyl azodicarboxylate.

Hydrolysis of the ester group R^{13} can be carried out using routine procedures, for example treatment of methyl and ethyl esters with aqueous sodium hydroxide, and treatment of tert-butyl esters with acids such as trifluoroacetic acid.

Preferred intermediates of formula (II) include
4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]- phenol,
4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenol,
4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenol,
4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenol,
4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenol,
2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenol,
2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenol,
4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenol,
2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenol,
2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenol,
2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenol,
2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenol

Compounds of formula (II) can be prepared by reaction of a compound of formula (IV) with a compound of formula (V) followed by deprotection of R^{14} when R^{14} is not equal to H :



(IV)

$Z-L^1$

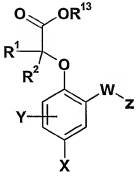
(V)

in which X, Y and Z are as defined in formula (I) or are protected derivatives thereof, V is S, NR^6 or O. R^{14} is H or a suitable protecting group, for example benzyl, L^1 is iodide, bromide, chloride, fluoride or activated alcohol such as triflate.
The reaction can be carried out in a suitable solvent such as 1-methyl-2-pyrrolidinone with a base such as potassium carbonate, preferably at elevated temperatures. The reaction may also be catalysed with palladium or copper catalysts.

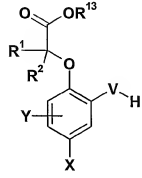
Preferred intermediates of formula (V) include
3-Chloro-4-fluorophenyl methyl sulfone,

3-Chloro-4-fluorophenyl ethyl sulfone

The sequence of the steps above may be changed, for example a compound of formula (VI) may be formed by the reaction of a compound of formula (VII) with a compound of formula (V).



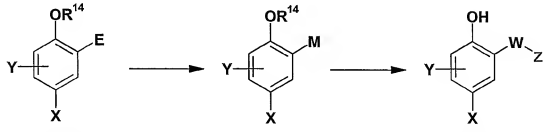
(VI)



(VII)

Preferred intermediates of formula (VII) include
2-(4-Chloro-2-hydroxyphenoxy)-2-methylpropanoic acid,
(4-Fluoro-2-hydroxyphenoxy)acetic acid,
2-(4-Fluoro-2-hydroxyphenoxy)-2-methylpropanoic acid,
(2S)-2-(4-Chloro-2-hydroxyphenoxy)propanoic acid

Compounds of formula (I) can be prepared from a compound of formula (VIII) by formation of an organometallic (IX) followed by reaction with an electrophile such as (X) or (XI), then deprotection of R^{14} as outlined in Scheme I.



(VIII) (IX) (II)

Scheme 1

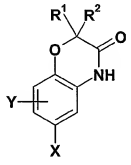
(X)

(XI)

in which X, Y are as defined in formula (I) or are protected derivatives thereof, W is defined as CR^1OR^2 or CR^1R^2, R^{13} is as defined in formula (IV), E is hydrogen or halogen and M is a metal such as Na or Li. For example when R^{14} is benzyl and E is bromine, butyl lithium can be used to form the intermediate (IX) where M = Li. The reaction is performed at −78°C in THF, then quenched with an electrophile such as (X) or (XI). When R^2=OH, this may be removed by reduction, for example hydrogenation with Pd/C. The protecting group R^{14} may then be removed

Compounds of formula (IV), where V = S can be prepared by reaction of a compound of formula (IX) with elemental sulphur.

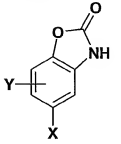
Compounds of formula (I), where W = N can be prepared by reaction of a compound of formula (XII) with a compound of formula (V)



(XII)

in which X, Y, R^1 and R^2 are as defined in formula (I) or are protected derivatives thereof, The reaction can be carried out in a suitable solvent such as 1-methyl-2-pyrrolidinone with a base such as potassium carbonate, preferably at elevated temperatures.

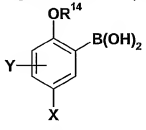
Compounds of formula (II), where W = N can be prepared by reaction of a compound of formula (XIII) with a compound of formula (V).



(XIII)

The reaction can be carried out in a suitable solvent such as 1-methyl-2-pyrrolidinone with a base such as potassium carbonate, preferably at elevated temperatures.

Compounds of formula (II), where W = C can be prepared by reaction of a compound of formula (XIV) with a compound of formula (XV)

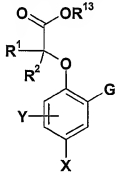


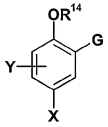
(XIV) (XV)

in which X, Y, R^1, R^2, R^{14}, Z and L are as defined as above or are protected derivatives thereof,

The reaction can be carried out in a suitable solvent such as ethylene glycoldimethylether with a base such as sodium carbonate and a palladium catalyst, preferably at elevated temperatures.

Compounds of formula (I) and compound of formula (II), where can be prepared by reaction of a compound of formula (XVI) or a compound of formula (XVII) with a compound of formula (XVIII)





(XVI) (XVII) (XVIII)

in which X, Y, R^1, R^2, R^{13}, R^{14}, Z and W are as defined as above or are protected derivatives thereof, G is halogen, triflate or boronic acid. The reaction can be carried out in a suitable solvent such as iso-propanol with a base such as potassium carbonate and a metal catalyst, such as copper, preferably at elevated temperatures.

In a further aspect, the present invention provides the use of a novel compound of formula (I)/(IA), and pharmaceutically acceptable salt or solvate thereof for use in therapy.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused

by excessive or unregulated production of PGD_2 and its metabolites. Examples of such conditions/diseases include:

(1) (respiratory tract) - obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness ; chronic obstructive pulmonary disease (COPD) ; bronchitis , including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

(2) (bone and joints) arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to e.g. congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthopathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositits and polymyositis; polymalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides ineluding giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa,

microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthalgias, tendonititides, and myopathies.

(3) (skin) psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions.

(4) (eyes) blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial.

(5) (gastrointestinal tract) glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn®s disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema).

(6) (abdominal) hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic.

(7) (genitourinary) nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female).

(8) (Allograft rejection) acute and chronic following, for example, transplantation of

kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

(9) (CNS) Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes.

(10) Other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome.

(11) Other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes.

(12) (Cardiovascular); atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis , inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (e.g. syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins.

(13) (Oncology) treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma ; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes.

(14) Diseases associated with raised levels of PGD_2 or its metabolites.

Thus, the present invention provides a compound of formula (IA), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds (I)/(IA) of the invention are used to treat diseases in which the chemokine receptor belongs to the CRTh2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma, rhinitis and other diseases in which raised levels of PGD_2 or its metabolites. It is preferred that the compounds of the invention are used to treat asthma or rhinitis.

In a further aspect, the present invention provides the use of a compound of formula (I)/(IA), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

The invention further relates to combination therapies wherein a compound of formula (1)/(IA) or a pharmaceutically acceptable salt, solvate or *in vivo* hydrolysable ester thereof, or a pharmaceutical composition or formulation comprising a compound of formula (1)/(IA) is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed .

In particular, for the treatment of the inflammatory diseases rheumatoid arthritis, psoriasis, inflammatory bowel disease, COPD, asthma and allergic rhinitis the compounds of the invention may be combined with agents such as tumour necrosis factor alpha (TNF-α) inhibitors such as anti-TNF monoclonal antibodies (for example Remicade, CDP-870 and adalimumab) and TNF receptor immunoglobulin molecules (such as Enbrel); non-selective cyclo-oxygenase (COX)-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); glucocorticosteroids (whether administered by topical,oral, intramuscular, intravenous, or intra-articular routes); methotrexate, lefunomide; hydroxychloroquine, d-penicillamine, auranofin or other parenteral or oral gold preparations.

The present invention still further relates to the combination of a compound of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-

761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-tert-butylphenol hydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2-cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to the combination of a compound of the invention together with a receptor antagonist for leukotrienes(LT)B4, LTC4, LTD4, and LTE4. selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention together with a phosphodiesterase (PDE) inhibitor such as the methylxanthanines including theophylline and aminophylline; and selective PDE isoenzyme inhibitors including PDE4 inhibitors and inhibitors of the isoform PDE4D, and inhibitors of PDE5.

The present invention still further relates to the combination of a compound of the invention together with histamine type 1 receptor antagonists such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, and mizolastine applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention together with a gastroprotective histamine type 2 receptor antagonist.

The present invention still further relates to the combination of a compound of the invention with antagonists of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention together with an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride, and ethylnorepinephrine hydrochloride.

The present invention still further relates to the combination of a compound of the invention together with anticholinergic agents including muscarinic receptor (M1, M2, and

M3) antagonists such as atropine, hyoscine, glycpyrrrolate, ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol .

The present invention still further relates to the combination of a compound of the invention together with a chromone, including sodium cromoglycate and nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the invention together with an inhaled glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide, and mometasone furoate.

The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12.

The present invention still further relates to the combination of a compound of the invention together with modulators of chemokine receptor function such as antagonists of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the $C-X_3-C$ family.

The present invention still further relates to the combination of a compound of the invention together with a cytokine or modulator of cytokine function, including alpha-, beta-, and gamma-interferon; interleukins (IL) including IL1 to 15, and interleukin antagonists or inhibitors, including agents which act on cytokine signalling pathways.

The present invention still further relates to the combination of a compound of the invention together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

The present invention still further relates to the combination of a compound of the invention together with other systemic or topically-applied anti-inflammatory agents including thalidomide and derivatives, retinoids, dithranol, and calcipotriol.

The present invention still further relates to the combination of a compound of the invention together with an antibacterial agent including penicillin derivatives, tetracyclines, macrolides, beta-lactams, flouroquinolones, and inhaled aminoglycosides; and antiviral agents including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir; amantadine, rimantadine; ribavirin; zanamavir and oseltamavir; protease inhibitors such as indinavir, nelfinavir, ritonavir, and saquinavir; nucleoside reverse transcriptase inhibitors such as didanosine, lamivudine, stavudine, zalcitabine, zidovudine; non-nucleoside reverse transcriptase inhibitors such as nevirapine, efavirenz.

The present invention still further relates to the combination of a compound of the invention together with cardiovascular agents such as calcium channel blockers, beta-adrenoceptor blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-2 receptor antagonists; lipid lowering agents such as statins, and fibrates; modulators of blood cell morphology such as pentoxyfylline; thrombolytics, and anticoagulants including platelet aggregation inhibitors.

The present invention still further relates to the combination of a compound of the invention together with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention together with agents for the treatment of acute and chronic pain, including centrally and peripherally-acting analgesics such as opioid analogues and derivatives, carbamazepine, phenytoin, sodium valproate, amitryptiline and other antidepressant agents, and non-steroidal anti-inflammatory agents.

The present invention still further relates to the combination of a compound of the invention together with parenterally or topically-applied local anaesthetic agents such as lignocaine.

The present invention still further relates to the combination of a compound of the invention together with (i) tryptase inhibitors; (ii) platelet activating factor (PAF) antagonists; (iii) interleukin converting enzyme (ICE) inhibitors; (iv) IMPDH inhibitors; (v) adhesion molecule inhibitors including VLA-4 antagonists; (vi) cathepsins; (vii) MAP kinase inhibitors; (viii) glucose-6 phosphate dehydrogenase inhibitors; (ix) kinin-B.sub1. - and B.sub2. -receptor antagonists; (x) anti-gout agents, e.g., colchicine; (xi) xanthine oxidase inhibitors, e.g., allopurinol; (xii) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone; (xiii) growth hormone secretagogues; (xiv) transforming growth factor (TGFβ); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) Tachykinin NK.sub1. and NK.sub3. receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; (xx) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892; (xxi) TNF□ converting enzyme inhibitors (TACE); (xxii) induced nitric oxide synthase inhibitors (iNOS) or (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (CRTH2 antagonists) (xxiv) inhibitors of P38

The compounds of the present invention may also be used in combination with anti-osteoporosis agents including hormonal agents such as raloxifene, and biphosphonates such as alendronate.

The compounds of the invention may also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAIDs) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics, and intra-articular therapies such as corticosteroids and hyaluronic acid derivatives, and nutritional supplements such as glucosamine.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of cancer. Suitable agents to be used in combination include:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine and paclitaxel; antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecins);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab and the anti-erbb1 antibody cetuximab [C225]) , farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin αvβ3 function and angiostatin);

(vi) vascular damaging agents such as combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;
(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;
(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and
(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating diseases mediated by PGD2 or its metabolites wherein the prostanoid binds to its receptor (especially CRTh2 receptor), which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I), prodrugs and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

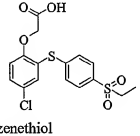
The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:
(i) when given, ^{1}H NMR data is quoted in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;
(ii) mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;
(iii) the title compounds of the examples and methods were named using the ACD/name (version 6.0) from Advanced Chemical Development Inc, Canada;
(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry,

NovaPak or Ex-Terra reverse phase silica column;
(v) solvents were dried with $MgSO_4$ or Na_2SO_4
(vi) final compounds were prepared as the free acid or a suitable salt such as sodium
(vii) the following abbreviations are used:

EtOAc	Ethylacetate
DCM	Dichloromethane
NMP	N-methylpyrrolidine
DMF	N,N-dimethylformamide
THF	tetrahydrofuran
mcpba	3-chloroperoxybenzoic acid (Aldrich 77% max)
$Pd(dppf)Cl_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane
RT	room temperature

Example 1
[4-Chloro-2-[[4-(ethylsulfonyl)phenyl]thio]phenoxy]- acetic acid, sodium salt



(i) 5-Chloro-2-methoxy-benzenethiol
Triphenylphosphine (11.4g) was added portionwise to a stirred solution of 5-chloro-2-methoxybenzenesulphonyl chloride (3.0g) in THF (30ml). Water (4ml) was added and the mixture stirred at RT for 2h, afterwhich the reaction was diluted with water (25ml) then 2M sodium hydroxide solution and washed with ether. The aqueous layer was acidified with 2M hydrochloric acid and extracted with ethylacetate. The organic layer was dried and evaporated under reduced pressure, yield 3.1g.
MS: ESI (-ve) 173 (M-1)

(ii) 4-Chloro-2-[[4-(ethylsulfonyl)phenyl]thio]-1-methoxy- benzene
Potassium carbonate (0.315g) was added to a stirred solution of the product from step (i) (0.4g) and ethyl-(4-bromo-phenyl)-sulfone (0.285g) in NMP (10ml) and the mixture heated at 90°C for 1h. The mixture was partitioned between water/ethylacetate, the organics separated, dried, and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 25% ethylacetate/isohexane. Yield 0.4g

^{1}H NMR $CDCl_3$: δ 7.76-6.91 (7H, m); 3.81 (3H, s) ; 3.13-3.06 (2H, q) ; 1.30-1.22 (3H, t).

(iii) 4-Chloro-2-[[4-(ethylsulfonyl)phenyl]thio]- phenol

A solution of boron tribromide (1M in DCM, 2.3ml) was slowly added to a stirred solution of the product from step (ii) (0.4g) in DCM (20ml) at 0°C. After 0.5h a further 4ml of boron tribromide solution was added and the mixture stirred for 1h. The reaction was quenched with crushed ice and partitioned between water and DCM. The organics separated, dried, and evaporated under reduced pressure, yield 0.3g.

MS: ESI (-ve) 327 (M-1)

(iv) [4-Chloro-2-[[4-(ethylsulfonyl)phenyl]thio]phenoxy]- acetic acid, 1,1-dimethylethyl ester

A mixture of the product from step (iii) (0.3g), tert-butylbromoacetate (0.15ml) and potassium carbonate (0.13g) in DMF (20ml) was stirred at RT overnight. The mixture was partitioned between water and ethylacetate, the organics separated, dried, and evaporated under reduced pressure. Yield 0.55g

MS: ESI (+ve) 460 ($M+NH_4$)

(v) [4-Chloro-2-[[4-(ethylsulfonyl)phenyl]thio]phenoxy]- acetic acid, sodium salt

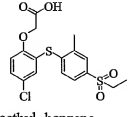
Trifluoroacetic acid (10ml) was added to a solution of the product from step (iv) (0.55g) in DCM (10ml) and the mixture stirred at RT for 1h. The mixture was evaporated under reduced pressure and the residue purified by reverse phase HPLC. The sodium salt was made using sodium hydroxide, yield 0.21 g.

^{1}H NMR DMSO-d6: δ 7.74-7.7](2H,m) ;7.49-6.90 (4H, m) ; 6.90-6.88 (1H, d) ; 4.16 (2H, s) ; 3.26-3.22 (2H, q) ; 1.11-1.06 (3H, t).

MS: ESI (-ve) 385 (M-1)

Example 2

[4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]phenoxy]- acetic acid, sodium salt



(i) 1-Bromo-4-(ethylthio)-2-methyl- benzene

Bromine (2.2ml) was added to a solution of 1-(ethylthio)-3-methylbenzene (6.6g) in acetic acid (20ml) at 0°C. The mixture was stirred at RT for 2h then the solvent removed under

reduced pressure. The residue was purified by chromatography on silica eluting with DCM. Yield 6.6g
MS: APCI (+ve): 247/9 (M+1)

(ii) 1-Bromo-4-(ethylsulfonyl)-2-methyl-benzene
3-Chloroperoxybenzoic acid (70% purity, 11.8g) was added to a solution of the product from step (i) (5g) in DCM (60ml) and stirred at RT for 4h. The mixture was partitioned between DCM/aq. sodium metabisulphite solution, the organics washed with aq. sodium hydrogencarbonate solution, water, dried and evaporated under reduced pressure. Yield 5.73g
^{1}H NMR $CDCl_3$: δ 7.76-7.73 (2H, m) ; 7.58-7.56 (1H, m) ; 3.10 (2H, q) ; 2.49 (3H, s) ; 1.28 (3H, t)

(iii) 4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]-1-methoxy- benzene
The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (ii). Yield 0.25g
^{1}H NMR $CDCl_3$ δ 7.70-6.91(6H, m) ;3.82 (3H, s) ; 3.13-3.06 (2H, q) ; 2.48 (3H, s) ; 1.30-1.22 (3H, t).

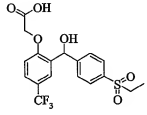
(iv) 4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]- phenol
The subtitle compound was prepared by the method of example 1 step (iii) using the product from step (iii). Yield 0.3g
MS: ESI (-ve) 341 (M-1)

(v) [4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]phenoxy] acetic acid-, 1,1-dimethylethyl ester
The subtitle compound was prepared by the method of example 1 step (iv) using the product from step (iv). Yield 0.5g
MS: ESI (+ve) 474 ($M+NH_4$)

(vi) [4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]phenoxy]- acetic acid, sodium salt
The title compound was prepared by the method of example 1 step (v) using the product from step (v). Yield 0.225g
^{1}H NMR DMSO-d6: δ 7.73-7.72(1H, d) 7.55-7.52 (1H, dd) ; 7.41-7.38 (1H, dd) ; 7.27-7.21 (2H, m) ; 6.89-6.87 (1H, d) ; 4.14 (2H, s) ; 3.27-3.22 (2H, q) ; 2.42 (3H, s) ; 1.10-1.07 (3H, t).
MS: ESI (-ve) 399 (M-1)

Example 3

[2-[[4-(Ethylsulfonyl)phenyl](hydroxy)methyl]-4-(trifluoromethyl)phenoxy]acetic acid



(i) Benzyl 2-bromo-4-(trifluoromethyl)phenyl ether

Benzyl bromide (21.4ml) was added to a stirred mixture of 2-bromo-4-trifluoromethylphenol (46.4g) and potassium carbonate (39g) in DMF (200ml). After 18h, the mixture was partitioned between diethylether and water, the organic layer washed with water , 2M sodium hydroxide solution, water, dried and the solvent evaporated under reduced pressure. Yield 58.7g

^{1}H NMR $CDCl_3$: δ 7.83 (1H, s) ; 7.51-7.32 (6H, m) ; 6.98 (1H, d) ; 5.21 (2H, s)

(ii) [2-(Benzyloxy)-5-(trifluoromethyl)phenyl][4-(ethylthio)phenyl]methanol

A solution of butyl lithium (1.6M in hexane, 1.03ml) was added to a stirred solution of the product from step (i) (0.5g) in diethylether (20ml) at –78°C. After 1h, 4-ethylsulfanyl-benzaldehyde (0.25g) was added and stirred for a further 1h. The reaction was quenched with water, extracted with diethylether and the organic layer dried, then evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 50% diethylether/isohexane. Yield 0.7g

^{1}H NMR $CDCl_3$: δ 7.36-7.13 (12H, m) ; 6.04-6.03 (1H, d) ; 5.05 (2H, s) ; 2.96-2.89 (2H, q) ; 2.64-2.62 (1H, d) ; 1.33-1.28 (3H, t).

MS: ESI (+ve) 401 (M-OH)

(iii) [2-(Benzyloxy)-5-(trifluoromethyl)phenyl][4-(ethylsulfonyl)phenyl]methanol

The subtitle compound was prepared by the method of example 2 step (ii) using the product from step (ii). Yield 0.45g

MS: ESI (+ve) 468 ($M+NH_4$)

(iv) 2-[[4-(Ethylsulfonyl)phenyl](hydroxy)methyl]-4-(trifluoromethyl)phenol

A mixture of the product from step (iii) (0.225g), 10% palladium on carbon (0.05g) in ethanol (20ml) was hydrogenated at 1Bar for 45min. After filtration the solvent was evaporated under reduced pressure. Yield 0.22g

MS: ESI (-ve) 359 (M-H)

(v) [2-[[4-(Ethylsulfonyl)phenyl](hydroxy)methyl]-4-(trifluoromethyl)phenoxy] acetic acid

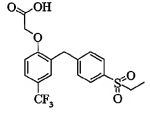
The title compound was prepared by the method of example 1 steps (iv) and (v) using the product from step (iv). Yield 0.045g

^{1}H NMR DMSO-d6: δ 7.80-7.52 (6H, m) ; 7.07-7.04 (1H, d) ; 6.12 (1H, s) ; 4.46 (2H, s) ; 3.41 (1H, bm) ; 3.27-3.20 (2H, q) ; 1.09-1.04 (3H, t).

MS: ESI (+ve) 436 (M+NH_4)

Example 4

[2-[4-(Ethylsulfonyl)benzyl]-4-(trifluoromethyl)phenoxy]acetic acid



(i) 2-[4-(Ethylsulfonyl)benzyl]-4-(trifluoromethyl)phenol

A mixture of the product from example 3 step (iii) (0.225g), 10% palladium on carbon (0.05g) and acetic acid (2 drops) in ethanol (20ml) was hydrogenated at 3Bar for 2h then 5Bar for 5h. After filtration the solvent was evaporated under reduced pressure. Yield 0.16g

MS: ESI (-ve) 343 (M-H)

(ii) [2-[4-(Ethylsulfonyl)benzyl]-4-(trifluoromethyl)phenoxy]acetic acid

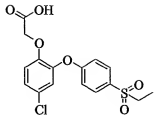
The title compound was prepared by the method of example 1 steps (iv) and (v) using the product from step (i). Yield 0.11g

^{1}H NMR DMSO-d6: δ 7.75-7.46 (6H, m) ; 6.92-6.89 (1H, d) ; 4.21 (2H, s) ; 4.10 (2H, s) ; 3.31-3.19(2H, q) ; 1.09-1.04 (3H, t).

MS: ESI (-ve) 401 (M-H)

Example 5

[4-Chloro-2-[4-(ethylsulfonyl)phenoxy]phenoxy]- acetic acid, sodium salt



(i) (4-Chloro-2-methoxyphenoxy)-acetic acid , ethyl ester

The subtitle compound was prepared by the method of example 1 step (iv) using ethyl bromoacetate and 4-chloro-2-methoxyphenol Yield 2.7g

^{1}H NMR $CDCl_3$: δ 6.88-6.74 (3H, m) ; 4.64 (2H, s) ; 4.29-4.21 (2H, q) ; 3.88-3.87 (3H, s) ; 1.30-1.20 (3H, t).

(ii) (4-Chloro-2-hydroxyphenoxy)- acetic acid

A mixture of the product from step (i) (2.7g) in 48% aqueous hydrogen bromide (30ml) was heated under reflux for 2h. The solvent was evaporated, the residue washed with water and dried, yield 1.7g.

^{1}H NMR DMSO-d6: δ 6.89-6.72 (3H, m) ; 4.66 (2H, m) ; 3.79 (1H, s).

(iii) [4-Chloro-2-[4-(ethylsulfonyl)phenoxy]phenoxy]- acetic acid, sodium salt

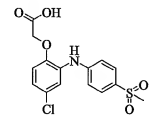
Cesium carbonate (0.2g) was added to a stirred mixture of the product from step (ii) (0.3g), ethyl-(4-bromo-phenyl)-sulfone (0..37g) and copper iodide (5mol%) in NMP (20ml) and the mixture heated at 170°C (oil bath temp.) for 10h. The mixture was quenched with 1M sodium hydroxide solution and extracted with ethylacetate. The aqueous layer was acidified with hydrochloric acid and extracted with ethylacetate. The organic extract was dried and evaporated under reduced pressure. The residue was purified by reverse phase HPLC, the sodium salt was formed using sodium hydroxide. Yield 0.068g

^{1}H NMR DMSO-d6 : δ 7.81-6.91(7H, m) ; 4.06 (2H, s) ; 3.26-3.21 (2H, q) ; 1.11-1.08 (3H, t).

MS: ESI (-ve) 369 (M-H)

Example 6

[4-Chloro-2-[[4-(methylsulfonyl)phenyl]amino]phenoxy]- acetic acid



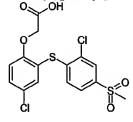
(i) (4-Chloro-2-nitrophenoxy)- acetic acid, ethyl ester
The subtitle compound was prepared by the method of example 1 step (iv) using ethyl bromoacetate and 4-chloro-2-nitrophenol Yield 1.4g

(ii) 6-Chloro-2*H*-1,4-benzoxazin-3(4*H*)-one
Iron powder (1.4g) was added to a solution of the product from step (i) (1.4g) in acetic acid (30ml) and the mixture stirred at RT for 1h. The mixture was filtered and the filtrate evaporated under reduced pressure. Yield 0.44g
^{1}H NMR DMSO-d6: δ 8.43 (1H, m) ; 6.92-6.81 (3H, m) ; 4.61 (2H, s).

(iii) [4-Chloro-2-[[4-(methylsulfonyl)phenyl]amino]phenoxy]- acetic acid
Potassium carbonate (0.265g) was added to a solution of the product from step (ii) (0.44g) and 4-fluorophenyl methyl sulfone (0.331g) in NMP (20ml) and the mixture heated at 120°C for 16h. The reaction was diluted with water and extracted with ethylacetate, the organics were dried and evaporated under reduced pressure. The residue was purified by reverse phase HPLC, yield 0.096g.
^{1}H NMR DMSO-d6: δ 11.33 (1H, s) ; 7.72-7.69 (2H, d) ; 7.31-7.30 (1H, m) ; 7.20-7.00 (3H, m) ; 6.92-6.89 (1H, d) ; 4.14 (2H, s) ; 3.11 (3H, s)
MS: APCI (+ve) 356 (M+H)

Example 7

(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid



(i) 3-Chloro-4-fluorophenyl methyl sulfide
Iodomethane (1.15ml) was added to a stirred mixture of 3-chloro-4-fluoro-benzenethiol (3.0g), potassium carbonate (2.48g) in DMF (20ml) and left overnight. The reaction was diluted with water and extracted with diethylether, the organics were dried and evaporated under reduced pressure, yield 4.3g.
1H NMR: $CDCl_3$: δ 7.31-7.14 (2H, m), 7.13-7.03 (1H, m), 3.23-3.21 (3H, s).

(ii) 3-Chloro-4-fluorophenyl methyl sulfone
The subtitle compound was prepared by the method of example 2 step (ii) using the product from step (i). Yield 3.8g

1H NMR: $CDCl_3$: δ 8.06-8.03 (1H, m), 7.89-7.84 (1H, m), 7.38-7.32 (1H, m), 3.08 (3H, s).

(iii) 4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenol

The subtitle compound was prepared by the method of example 1 steps (i)-(iii) using the product from step (ii).

MS: ESI(-ve) 347(M-1)

(iv) (4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid

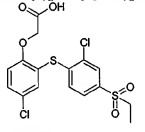
The title compound was prepared by the method of example 1 steps (iv)-(v) using the product from step (iii). Yield 0.158g

1H NMR: DMSO-d6: δ 13.12 (1H, bs), 7.997-7.99 (1H, m), 7.69-7.58 (3H, m), 7.18-6.97 (2H, d), 4.80 (2H, s), 3.24 (3H, s).

MS: ESI(-ve) 406(M-1)

Example 8

(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)acetic acid, sodium salt



(i) 3-Chloro-4-fluorophenyl ethyl sulfone

The subtitle compound was prepared by the method of example 7 step (i)-(ii) using iodoethane.

1H NMR: $CDCl_3$: δ 8.01-7.98 (1H, d), 7.84-7.79 (1H, m), 7.37-7.31 (1H, m), 3.17-3.09 (2H, q), 1.33-1.26 (3H, t).

(ii) 4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenol

The subtitle compound was prepared by the method of example 1 steps (i)-(iii) using the product from step (i).

MS: ESI(-ve) 362(M-1)

(iii) (4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)acetic acid, sodium salt

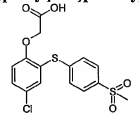
The title compound was prepared by the method of example 1 steps (iv)-(v) using the product from step (ii), yield 0.19g.

1H NMR: DMSO-d6: δ 7.90-7.89 (1H, d), 7.61-7.58 (1H, d), 7.53-7.49 (2H, m), 7.29-7.27 (1H, d), 6.95-6.92 (1H, d), 4.17 (2H, s), 3.34-3.30 (2H, m), 1.14-1.08 (3H, m).

MS: ESI(-ve) 420(M-1)

Example 9

(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid



(i) 4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenol

The subtitle compound was prepared by the method of example 1 steps (i)-(iii) using methyl-(4-bromo-phenyl)sulphone, yield 0.98g.

MS: ESI(-ve) 313(M-1)

(ii) tert-Butyl (4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)acetate

The subtitle compound was prepared by the method of example 1 step (iv) using the product from step (i), yield 0.95g.

MS: ESI(+ve) 443($M+NH_4$)

(iii) (4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid

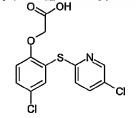
The title compound was prepared by the method of example 1 step (v) using the product from step (ii), yield 0.165g.

1H NMR: DMSO-d6: δ 7.80-7.77 (2H, m), 7.47-7.41 (3H, m), 7..38-7.37 (1H, d), 6.93-6.91 (1H, d), 4.27 (2H, s), 3.19 (3H, s).

MS: ESI(-ve) 371(M-1)

Example 10

{4-Chloro-2-[(5-chloropyridin-2-yl)thio]phenoxy}acetic acid



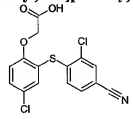
The title compound was prepared by the general method of example 1.

1H NMR: DMSO-d6: δ 8.46-8.45 (1H, m), 7.76-7.73 (1H, d), 7.59-7.58 (1H, d), 7.52-7.50 (1H, d), 7.10-7.04 (2H, m), 4.74 (2H, s).

MS: ESI(-ve) 329(M-1)

Example 11

{4-Chloro-2-[(2-chloro-4-cyanophenyl)thio]phenoxy}acetic acid



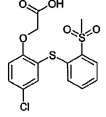
The title compound was prepared by the general method of example 1.

1H NMR: DMSO-d6: δ 8.07 (1H, d), 7.62-7.57 (3H, m), 7.16-7.12 (1H, m), 6.90-6.87 (1H, d), 4.75 (2H, s).

MS: ESI(-ve) 353(M-1)

Example 12

(4-Chloro-2-{[2-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid



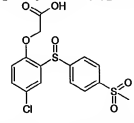
The title compound was prepared by the general method of example 1.

1H NMR: DMSO-d6: δ 13.05 (1H, bs), 7.94-7.92 (1H, d), 7.60-7.42 (4H, m), 7.42-7.08 (2H, m), 4.67 (2H, s), 3.44 (3H, s).

MS: ESI(-ve) 371(M-1)

Example 13

(4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfinyl}phenoxy)acetic acid, sodium salt



(i) tert-Butyl (4-chloro-2-{[4-(methylsulfonyl)phenyl]sulfinyl}phenoxy)acetate

3-Chloroperoxybenzoic acid (70% purity, 0.2g) was added to a solution of the product from example 9 step (ii) (0.35g) in DCM (10ml) and stirred at 0°C for 1h. The mixture was partitioned between DCM/aq. sodium metabisulphite solution, the organics washed with aq. sodium hydrogencarbonate solution, water, dried and evaporated under reduced pressure. Yield 0.34g

MS: APCI(-ve) 388(M-tert-butyl)

(ii) (4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfinyl}phenoxy)acetic acid, sodium salt

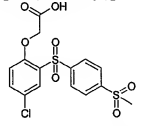
The title compound was prepared by the method of example 1 step (v) using the product from step (i), yield 0.071g.

1H NMR: DMSO-d6: δ 8.33-8.31 (2H, d), 8.01-7.99 (2H, d), 7.56-7.55 (1H, d), 7.45-7.42 (1H, d), 6.95-6.93 (1H, d), 4.30-4.22 (2H, q), 3.24 (3H, s).

MS: APCI(+ve) 389(M+1)

Example 14

(4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfonyl}phenoxy)acetic acid



(i) tert-Butyl (4-chloro-2-{[4-(methylsulfonyl)phenyl]sulfonyl}phenoxy)acetate

3-Chloroperoxybenzoic acid (70% purity, 0.4g) was added to a solution of the product from example 9 step (ii) (0.35g) in DCM (10ml) and stirred at 0°C for 1h. The mixture was partitioned between DCM/aq. sodium metabisulphite solution, the organics washed with aq. sodium hydrogencarbonate solution, water, dried and evaporated under reduced pressure. Yield 0.36g

(ii) (4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfonyl}phenoxy)acetic acid

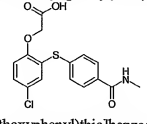
The title compound was prepared by the method of example 1 step (v) using the product from step (i), yield 0.108g.

1H NMR: DMSO-d6: δ 8.35-8.32 (2H, d), 8.10-8.06 (2H, d), 7.96-7.95 (1H, d), 7.71-7.68 (1H, d), 7.08-7.06 (1H, d), 4.46 (2H, s), 3.27 (3H, s).

MS: ESI(-ve) 403(M-1)

Example 15

[4-Chloro-2-({4-[(methylamino)carbonyl]phenyl}thio)phenoxy]acetic acid



(i) Ethyl 4-[(5-chloro-2-methoxyphenyl)thio]benzoate

A mixture of the product from example 1 step (i) (0.5g), ethyl-4-fluoro-benzoate (0.32ml), 25%wt potassium fluoride on alumina (1.25g) and 18-crown-6 (8mg) in DMSO (20ml) was heated at 140°C for 4h. The mixture was cooled, diluted with ethylacetate (100ml), filtered and the filtrate washed with water, brine, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with DCM/isohexane (2:1), yield 0.24g.
MS: ESI(+ve) 323(M+1)

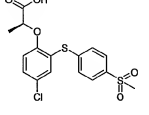
(ii) 4-[(5-Chloro-2-methoxyphenyl)thio]benzoic acid
A mixture of the product from step (i) (0.24g), lithium hydroxide (0.036g) in methanol (30ml) and water (5ml) was stirred at RT overnight then acidified with 2M hydrochloric acid. The mixture was extracted with ethylacetate, the organics dried and evaporated under reduced pressure, yield 0.23g
MS: ESI(-ve) 293(M-1)

(iii) 4-[(5-Chloro-2-methoxyphenyl)thio]-N-methylbenzamide
A mixture of the product from step (ii) (0.23g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.22g), 1-hydroxybenzotriazole (0.15g), N,N-diisopropylethylamine (0.3g) and methylamine (2M in THF, 0.78ml) in DMF (10ml) was stirred at RT overnight. Water was added and the mixture extracted with ethylacetate, the organics were dried and evaporated under reduced pressure, yield 0.24g.
MS: ESI(+ve) 308(M+1)

(iv) [4-Chloro-2-({4-[(methylamino)carbonyl]phenyl}thio)phenoxy]acetic acid
The title compound was prepared by the method of example 1 steps (iii)-(v) using the product from step (iii), yield 0.119g.
1H NMR: DMSO-d6: δ 13.12 (1H, bs), 8.47-8.46 (1H, m), 7.82-7.80 (2H, m), 7.40-7.34 (3H, m), 7.04-7.01 (2H, m), 4.78 (2H, s), 2.66 (3H, s).
MS: ESI(-ve) 350(M-1)

Example 16

(2S)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid



(i) tert-Butyl (2S)-2-(4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy) propanoate

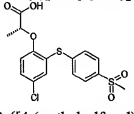
Diisopropyl azodicarboxylate (0.19ml) was added to a stirred solution of the product from example 9 step (i) (0.3g), triphenylphosphine (0.25g), R-tert-butyl lactate (0.14g) in THF (10ml). After 2h the solvent was evaporated under reduced pressure and the residue purified by chromatography on silica eluting with diethylether/isohexane (2:1), yield 0.6g.
MS: ESI(+ve) 460(M+NH4)

(ii) (2S)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid

The title compound was prepared by the method of example 1 step (v) using the product from step (i), yield 0.15g.
1H NMR: DMSO-d6: δ 7.82-7.80 (2H, m), 7.46-7.39 (4H, m), 6.95-6.93 (1H, d), 4.66-4.64 (1H, m), 3.18 (3H, s), 1.25-1.23 (3H, d).
MS: ESI(-ve) 385 (M-1)

Example 17

(2R)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid



(i) Methyl (2R)-2-(4-chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoate

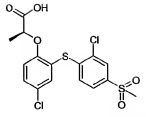
The subtitle compound was prepared by the method of example 16 step (i) using S-methyl lactate, yield 0.35g.
MS: ESI(+ve) 418 (M+NH4)

(ii) (2R)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid

The title compound was prepared by the method of example 15 step (ii) using the product from step (i), yield 0.13g.
1H NMR: DMSO-d6: δ 7.82-7.79 (2H, m), 7.47-7.40 (4H, m), 6.96-6.94 (1H, d), 4.70-4.67 (1H, q), 3.18 (3H, s), 1.26-1.12 (3H, d).
MS: ESI(-ve) 385 (M-1)

Example 18

(2S)-2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid, sodium salt



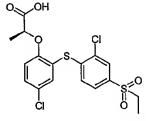
The title compound was prepared by the method of example 16 using the product from example 7 step (iii), yield 0.2g.

1H NMR: DMSO-d6: δ 7.96-7.95 (1H, m), 7.67-7.63 (1H, m), 7.49-7.45 (2H, m), 7.35-7.32 (1H, m), 6.93-6.90 (1H, d), 4.27-4.20(1H, q), 3.23 (3H, s), 1.17-1.06 (3H, d).

MS: ESI(-ve) 419/421 (M-1)

Example 19

(2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)propanoic acid, sodium salt



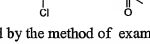
The title compound was prepared by the method of example 16 using the product from example 8 step (ii), yield 0.54g.

1H NMR: DMSO-d6: δ 7.90-7.89 (1H, m), 7.62-7.47 (3H, m), 7.30-7.28 (1H, d), 6.95-6.92 (1H, d), 4.35-4.32 (1H, q), 3.39-3.29 (2H, q), 1.13-1.05 (6H, d+t).

MS: ESI(-ve) 433 (M-1)

Example 20

2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)-2-methylpropanoic acid



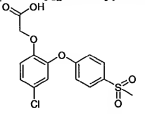
The title compound was prepared by the method of example 1 step (iv) using the product from example 7 step (iii) and tert-butyl-2-bromoisobutyrate, yield 0.028g.

1H NMR: DMSO-d6: δ 8.02-8.01 (1H, m), 7.73-7.69 (1H, m), 7.56-7.50 (2H, m), 7.12-6.95 (2H, d), 3.25 (3H, s), 1.33 (6H, s).

MS: ESI(-ve) 433/435 (M-1)

Example 21

{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}acetic acid, sodium salt



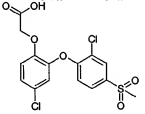
A mixture of the product from example 5 step (ii) (0.3g), methyl-(4-fluoro-phenyl)sulfone (0.226g) and potassium carbonate (0.18g) in NMP (20ml) was heated at 160°C for 2h. The mixture was partitioned between ethylacetate/2M hydrochloric acid, the organics separated, dried, and evaporated under reduced pressure. The residue was purified by reverse phase HPLC, the sodium salt formed from sodium hydroxide. Yield 0.103g

^{1}H NMR DMSO-d6: δ 7.85-7.80 (1H, d), 7.25-7.14 (5H, d), 6.95-6.91 (1H, d), 4.10 (2H, s), 3.17(3H, s).

MS: ESI(-ve) 355(M-1)

Example 22

{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid, sodium salt



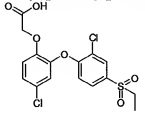
The title compound was prepared by the method of example 21 using the product from example 5 step (ii) and example 7 step (ii), yield 0.132g.

1H NMR: DMSO-d6: δ 8.05-8.04 (1H, m), 7.73-7.71 (1H, m), 7.28-7.25 (2H, m), 7.18-7.16 (1H, m), 6.96-6.94 (1H, m), 4.11 (2H, s), 3.24(3H, s).

MS: ESI(-ve) 389(M-1)

Example 23

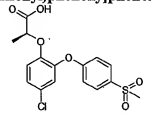
{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}acetic acid



The title compound was prepared by the method of example 21 using the product from example 5 step (ii) and example 8 step (i), yield 0.296g.
1H NMR: DMSO-d6: δ 8.00-7.99 (1H, d), 7.72-7.68 (1H, m), 7.34-7.32 (2H, m), 7.07-7.04 (2H, d), 4.41(2H, s), 3.39-3.29 (2H, q), 1.15-1.07 (3H, t).
MS: ESI(-ve) 403/405 (M-1)

Example 24

(2S)-2-{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid, sodium salt



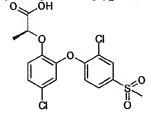
(i) 4-Chloro-1-methoxy-2-[4-(methylsulfonyl)phenoxy]benzene
The subtitle compound was prepared by the method of example 1 step (ii) using 5-chloro-2-methoxy-phenol, yield 0.35g.
1H NMR: $CDCl_3$: δ 7.88-7.85 (2H, d), 7.27-6.95 (5H, m), 3.78 (3H, s), 3.06-3.05 (3H, s).

(ii) 4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenol
The subtitle compound was prepared by the method of example 1 step (iii) using the product from step (i), yield 0.17g.
MS: APCI(-ve) 297(M-1)

(iii) (2S)-2-{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid, sodium salt
The title compound was prepared by the method of example 16 using the product from step (ii), yield 0.063g.
1H NMR: DMSO-d6: δ 7.85-7.80 (2H, m), 7.22-7.16 (4H, m), 6.93-6.90(1H, d), 4.19-4.12 (1H, q), 3.14 (3H, s), 1.11-1.06 (3H, d).
MS: ESI(-ve) 369(M-1)

Example 25

(2S)-2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid



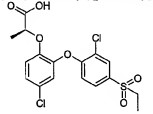
(i) 3-Chloro-4-(5-chloro-2-methoxyphenoxy)phenyl methyl sulfone
The subtitle compound was prepared by the method of example 1 step (ii) using the product from example 7 step (ii) and 5-chloro-2-methoxy phenol. Yield 4.0g
MS: ESI(+ve) 363($M+NH_4$)

(ii) 4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenol
The subtitle compound was prepared by the method of example 1 step (iii) using the product from step (i). Yield 3.0g
MS: ESI(-ve) 331(M-1)

(iii) (2S)-2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid
The title compound was prepared by the method of example 16 using the product from step (ii). Yield 0.206g
1H NMR: DMSO-d6: δ 8.09-8.08 (1H, m), 7.78-7.75 (1H, m), 7.39-7.32 (2H, m), 7.09-7.07 (1H, d), 7.00-6.98 (1H, d), 4.87-4.80 (1H, q), 3.24 (3H, s), 1.25-1.15 (3H, d).
MS: ESI(-ve) 403/405 (M-1)

Example 26

(2S)-2-{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}propanoic acid



(i) 4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]-1-methoxybenzene
The subtitle compound was prepared by the method of example 1 step (ii) using the product from example 8 step (i) and 5-chloro-2-methoxy phenol. Yield 3.30g
MS: ESI(+ve) 378($M+NH_4$)

(ii) 4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenol
The subtitle compound was prepared by the method of example 1 step (iii) using the product from step (i). Yield 3.10g
MS: ESI(-ve) 345(M-1)

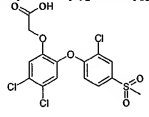
(iii) Methyl (2S)-2-{4-chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy} propanoate

The subtitle compound was prepared by the method of example 16 step (i) using the product from step (ii) and R-methyl lactate. Yield 2.30g
MS: ESI(+ve) 435($M+NH_4$)

(iv) (2S)-2-{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}propanoic acid
A mixture of the product from step (iii) (2.3g) and lithium hydroxide (0.303g) in water (10ml) and THF (10ml) was stirred at RT for 1h. The mixture was diluted with water, extracted with diethylether then the aqueous layer acidified by 2M hydrochloric acid and extracted with ethylacetate. The ethyl acetate layer was dried, evaporated under reduced pressure and the residue purified by RPHPLC.
1H NMR: DMSO-d6: δ 7.99-7.67 (2H, m), 7.33-6.95 (4H, m), 4.36-4.34 (1H, q), 3.35-3.29 (2H, q), 1.25-1.15 (6H, m).
MS: ESI (-ve) 417/419 (M-1)

Example 27

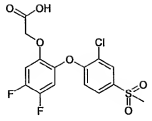
{4,5-Dichloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid



A mixture of sodium hydride (60% wt. disp. in oil, 0.223g) and 4,5-dichlorocatechol (1g) in DMF(10ml) was stirred at RT for 15min. tert-Butyl-bromoacetate (0.9ml) was added, stirred at RT for 2h then potassium carbonate (0.77g) and the product from example 7 step (ii) (0.7g) added and the mixture heated at 90°C for 14h. The mixture was partitioned between 2M sodium hydroxide solution and diethylether, the aqueous layer was acidified with 2M hydrochloric acid and extracted with ethylacetate. The ethylacetate layer was dried, evaporated under reduced pressure and the residue purified by RPHPLC. Yield 0.349g.
1H NMR: DMSO-d6: δ 8.06-7.71 (2H, m), 7.54 (1H, s), 7.27-7.13 (2H, m), 4.32.(2H, s), 3.24 (3H, s).
MS: ESI(-ve) 423/425 (M-1)

Example 28

{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4,5-difluorophenoxy}acetic acid



(i) 4,5-Difluoro-2-methoxyphenol

Sodium thiomethoxide (0.4g) was added to a solution of 1,2-difluoro-4,5-dimethoxybenzene (1.0g) in DMF (10ml) at RT, then heated at 100°C for 4h. A further 0.8g of sodium thiomethoxide was added, the mixture heated for a further 2h. The mixture was cooled, partitioned between ethylacetate/2M hydrochloric acid, the organics dried and evaporated under reduced pressure, yield 1.05g

(ii) tert-Butyl (4,5-difluoro-2-methoxyphenoxy)acetate

The subtitle compound was prepared by the method of example 1 step (iv) using the product from step (i), yield 0.75g.

1H NMR: $CDCl_3$: δ 6.76-6.70 (2H, m), 4.51 (2H, s), 3.84 (3H, s), 1.48 (9H, s).

(iii) (4,5-Difluoro-2-hydroxyphenoxy)acetic acid

A mixture of the product from step (ii) (0.75g) and lithium chloride (0.345g) in DMF(20ml) was heated at 150°C for 6h, cooled and partitioned between ethylacetate/2M hydrochloric acid. The organics were dried and evaporated under reduced pressure, yield 0.7g.

(iv) {2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4,5-difluorophenoxy}acetic acid

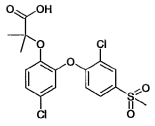
A mixture of sodium hydride (60% wt. disp. in oil, 0.275g) and the product from step (iii) (0.7g) in DMF(10ml) was stirred at RT for 15min. The product from example 7 step (ii) (0.715g) was added and the mixture heated at 85°C for 15h. The mixture was partitioned between 2M sodium hydroxide solution and diethylether, the aqueous layer was acidified with 2M hydrochloric acid and extracted with ethylacetate. The ethylacetate layer was dried, evaporated under reduced pressure and the residue purified by RPHPLC. Yield 0.076g.

1H NMR: DMSO-d6: δ 8.07 (1H, s), 7.76-7.73 (1H, m), 7.59-7.54 (1H, m), 7.43-7.38 (1H, m), 6.98-6.96 (1H, m), 4.69(2H, s), 3.24 (3H, s).

MS: ESI(-ve) 391 (M-1)

Example 29

2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}-2-methylpropanoic acid



(i) 2-(Benzyloxy)-4-chlorophenol

Sulfuryl chloride (0.965ml) was added to a stirred solution of 2-(benzyloxy)phenol (2.0g) in dry toluene (20ml) at 0°C. The mixture was warmed to RT and stirred overnight then cooled to 0°C and quenched with ice-water before extracting with ethylacetate. The organics were dried, evaporated under reduced pressure and the residue purified by chromatography on silica eluting with DCM/isohexane (1:1). Yield 1.5g

MS: ESI(-ve) 233 (M-1)

(ii) 2-[2-(Benzyloxy)-4-chlorophenoxy]-2-methylpropanoic acid

Powdered sodium hydroxide (0.253g) was added to a stirred mixture of the product from step (i) (1.5g) and 1,1,1-trichloro-2-methylpropanol (3.0g) in acetone (40ml) at 0°C. After stirring at RT for 1h the mixture was cooled to 0°C and a further portion of sodium hydroxide (0.253g) added. After repeating for a third time, the mixture was stirred at RT overnight, then quenched with 2M hydrochloric acid and extracted with ethylacetate. The organics were dried, evaporated under reduced pressure and the residue purified by chromatography on silica eluting with diethylether:isohexane (1:1). Yield 1.4g

(iii) 2-(4-Chloro-2-hydroxyphenoxy)-2-methylpropanoic acid

A mixture of the product from step (ii) (1.4 g) and 10% Pd/C (0.14g) in ethylacetate (30ml) was hydrogenated at 2Bar for 3h then filtered through celite. The filtrate was evaporated under reduced pressure, yield 0.6g.

MS: ESI(-ve) 229 (M-1)

(iv) 2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}-2-methylpropanoic acid

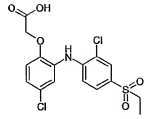
The title compound was prepared by the method of example 28 step (iv) using the product from step (iii). Yield 0.039g

1H NMR: DMSO-d6: δ 8.08-8.07 (1H, s), 7.78-7.75 (1H, m), 7.39-7.39 (1H, m), 7.28-7.25(1H, m), 7.06-6.98 (2H, m), 3.24 (3H, s), 1.22 (6H, s).

MS: ESI(-ve) 417 (M-1)

Example 30

(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)acetic acid



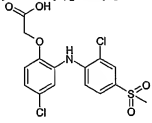
A mixture of the product from example 8 step (i) (0.21g), 6-chloro-2H-1,4-benzoxazin-3(4H)-one (0.15g) and potassium carbonate (0.23g) in DMF was heated in a microwave (CEM, 50W) at 120°C for 5min. The mixture was heated at 140°C for a further 5min, cooled and partitioned between ethylacetate/2M hydrochloric acid. The organics were separated, washed with brine, dried and evaporated under reduced pressure. The residue was purified by RPHPLC, yield 0.08g.

1H NMR: DMSO-d6: δ 8.82 (1H, s), 7.78 (1H, s), 7.57 (1H, d), 7.33(1H, s), 7.17 (1H, d), 7.10 (1H, d), 7.07 (1H, d), 4.51 (2H, s), 3.24 (2H, q), 1.10 (3H, t)

MS: APCI(-ve) 402 (M-1)

Example 31

(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)acetic acid



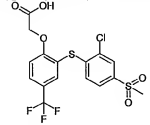
The title compound was prepared by the method of example 30 using the product from example 7 step (ii). Yield 1.54g

1H NMR: DMSO-d6: δ 13.14 (1H, s), 7.94 (1H, s), 7.87 (1H, s), 7.61 (1H, d), 7.35(1H, s), 7.22 (1H, d), 7.09 (1H, d), 6.99 (1H, d), 4.77 (2H, s), 3.18 (3H, s)

MS: APCI(+ve) 391(M+1)

Example 32

[2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid



(i) 2-(Benzyloxy)-5-(trifluoromethyl)benzenethiol

A solution of butyllithium (1.6M in hexanes, 18.5ml) was added dropwise to a stirred solution of 2-(benzyloxy)-5-trifluoromethylthiophenol (7.0g) in dry diethylether (40ml) at −78°C. After 40min elemental sulphur (0.68g) was added, the mixture was stirred at −78 C for 1h, quenched with 2M NaOH solution and extracted with diethylether. The aqueous layer was acidified, extracted with ethyl acetate, the ethyl acetate layer dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with diethylether:isohexane 1:6, yield 4.40g.

MS: ESI(-ve) 283 (M-1)

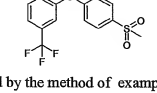
(ii) 4-{[2-(Benzyloxy)-5-(trifluoromethyl)phenyl]thio}-3-chlorophenyl methyl sulfone
The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (i) and the product from example 7 step (ii), yield 0.43g.
1H NMR: $CDCl_3$: δ 7.89-6.81(11H, m), 5.13(2H, s), 3.00 (3H, s).

(iii) 2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenol
The subtitle compound was prepared by the method of example 1 step (iii) using the product from step (ii), yield 0.22g.
MS: ESI(-ve) 381/383 (M-1)

(iv) [2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid
The title compound was prepared by the method of example 1 steps (iv-v) using the product from step (iii), yield 0.054g.
1H NMR: DMSO-d6: δ 7.998-7.99 (1H, s), 7.90-7.88 (2H, m), 7.67-7.65 (1H, d), 7.28-7.26 (1H, d), 7.03-7.01(1H, d), 4.77 (2H, s), 3.23(3H, s).
MS: ESI(-ve) 438 (M-1)

Example 33

(2S)-2-[2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy] propanoic acid, sodium salt

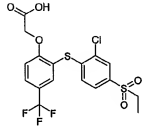


The title compound was prepared by the method of example 16 using the product from example 32 step (iii).

1H NMR: DMSO-d6: δ 7.97 (1H, s), 7.82-7.80 (2H, m), 7.66-7.65 (1H, m), 7.31-7.28 (1H, d), 7.10-7.07 (1H, d), 4.54-4.49 (1H, q), 2.99 (3H, s), 1.20-1.18 (3H, d).
MS: ESI(-ve) 453 (M-1)

Example 34

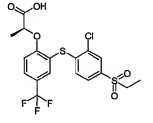
[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid, sodium salt



The title compound was prepared by the method of example 32 using the product from example 8 step (i).
1H NMR: DMSO-d6: δ 7.90-7.81 (3H, m), 7.59-7.56 (1H, d), 7.30-7.27 (1H, d), 7.10-7.08 (1H, d), 4.27 (2H, s), 3.39-3.29 (2H, q), 1.10-1.07 (3H, t).
MS: ESI(-ve) 453 (M-1)

Example 35

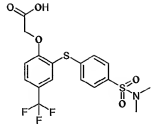
(2S)-2-[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy] propanoic acid, sodium salt



The title compound was prepared by the method of example 16 and example 32.
1H NMR: DMSO-d6: δ 7.90-7.78 (3H, m), 7.60-7.57 (1H, m), 7.37-7.35 (1H, d), 7.06-7.04 (1H, d), 4.37-4.35 (1H, q), 3.34-3.29 (2H, q), 1.14-1.05 (6H, d+t).
MS: ESI(-ve) 467 (M-1)

Example 36

[2-({4-[(Dimethylamino)sulfonyl]phenyl}thio)-4-(trifluoromethyl)phenoxy]acetic acid, sodium salt



(i) 4-Fluoro-N,N-dimethylbenzenesulfonamide

Dimethylamine hydrochloride (1.27g) was added to a solution of 4-fluoro-benzenesulphonyl chloride (3.0g) and N,N-diisopropylethylamine (5.37ml) in dichloromethane (30ml), the mixture was stirred at RT for 1h, diluted with water, extracted with dichloromethane, dried and evaporated under reduced, yield 3.0g.

(ii) [2-({4-[(Dimethylamino)sulfonyl]phenyl}thio)-4-(trifluoromethyl)phenoxy]acetic acid, sodium salt

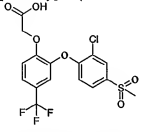
The title compound was prepared by the method of example 32 using the product from step (i).

1H NMR: DMSO-d6: δ 7.73-7.71 (1H, m), 7.62-7.60 (3H, m), 7.51-7.49 (2H, d), 7.04-7.02 (1H, d), 4.25 (2H, s), 2.58 (6H, s).

MS: ESI(-ve) 434 (M-1)

Example 37

[2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid



(i) Benzyl 2-fluoro-5-(trifluoromethyl)phenyl ether

A mixture of 5-(trifluoromethyl)-2-fluorophenol (2.0g), benzyl bromide (1.45ml) and potassium carbonate (1.65g) in dry DMF (20ml) was stirred at RT overnight. The mixture was quenched with water and the solid filtered and dried, yield 2.20g.

1H NMR: $CDCl_3$: δ 7.47-7.14 (8H, m), 5.16 (2H, s).

(ii) 2-(Benzyloxy)-1-methoxy-4-(trifluoromethyl)benzene

A solution of sodium methoxide in methanol (25%wt, 20ml) and the product from step (i) (1.20g) was heated at 100°C for 3h. The mixture was quenched with water (100ml) and the solid was filtered and dried, yield 1.28g.

1H NMR: $CDCl_3$: δ 7.46-6.91 (8H, m), 5.15 (2H, s), 3.19 (3H, s).

(iii) 2-Methoxy-5-(trifluoromethyl)phenol

The subtitle compound was prepared by the method of example 29 step (iii) using the product from step (ii), yield 0.70g.

MS: ESI(-ve) 191 (M-1)

(iv) [2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid

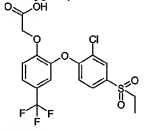
The title compound was prepared by the method of example 1 steps (ii-v) using the product from step (iii).

1H NMR: DMSO-d6: δ 8.08 (1H, m), 7.77-7.65 (3H, m), 7.33-7.30 (1H, d), 6.95-6.92 (1H, d), 4.79 (2H, s), 3.25 (3H, s).

MS: ESI(-ve) 423 (M-1)

Example 38

[2-[2-Chloro-4-(ethylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid



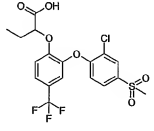
The title compound was prepared by the method of example 37 using the product from example 8 step (i).

1H NMR: DMSO-d6: δ 7.99 (1H, s), 7.68-7.54 (3H, m), 7.20-7.18 (1H, d), 7.11-7.09 (1H, d), 4.20 (2H, s), 3.35-3.30 (2H, q), 1.12-1.08 (3H, t).

MS: ESI(-ve) 437 (M-1)

Example 39

2-[2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]butanoic acid, sodium salt

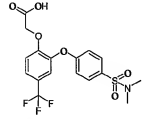


The title compound was prepared by the method of example 37 using ethyl-2-butyrate.

1H NMR: DMSO-d6: δ 8.05-8.04 (1H, s), 7.71-7.68 (1H, m), 7.57-7.56 (2H, m), 7.17-7.15 (1H, d), 7.05-7.03 (1H, d), 4.14-4.11 (1H, t), 3.20 (3H, s), 1.59-1.52 (2H, m), 0.52-0.49 (3H, t).
MS: ESI(-ve) 451 (M-1)

Example 40

[2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]acetic acid, sodium salt

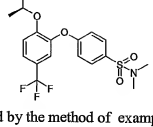


(i) 4-[2-Hydroxy-5-(trifluoromethyl)phenoxy]-N,N-dimethylbenzenesulfonamide
The subtitle compound was prepared by the method of example 1 steps (ii-iii) using the products from example 37 step (iii) and example 36 step (i), yield 0.95g.
MS: ESI (-ve) 360 (M-1).

(ii) [2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]acetic acid, sodium salt
The title compound was prepared by the method of example 1 steps (iv-v) using the product from step (i)
1H NMR: DMSO-d6: δ 7.68-7.66 (2H, m), 7.56-7.54 (1H, d), 7.50-7.49 (1H, m), 7.20-7.07 (3H, m), 4.21 (2H, s), 2.58 (6H, s).
MS: ESI(-ve) 418 (M-1)

Example 41

(2S)-2-[2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]propanoic acid, sodium salt

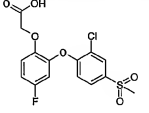


The title compound was prepared by the method of example 16 using the product from example 40 step (i).

1H NMR: DMSO-d6: δ 7.68-7.64 (2H, m), 7.55-7.51 (2H, m), 7.22-7.20 (2H, m), 7.07-7.05 (1H, d), 4.35-4.30 (1H, m), 2.57 (6H, s), 1.12-1.09 (3H, d).
MS: ESI(-ve) 432 (M-1)

Example 42

{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid



(i) tert-Butyl (4-fluoro-2-methoxyphenoxy)acetate

The subtitle compound was prepared by the method of example 1 step (iv) using 4-fluoro-2-methoxyphenol, yield 1.0g.
MS: ESI(-ve) 201 (M-t-butyl)

(ii) (4-Fluoro-2-hydroxyphenoxy)acetic acid

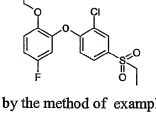
The subtitle compound was prepared by the method of example 28 step (iii) using the product from step (i), yield 0.72g.
MS: ESI(-ve) 185 (M-1)

(iii) {2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid

The title compound was prepared by the method of example 1 step (ii) using the product from step (ii) and the product from example 7 step (ii).
1H NMR: DMSO-d6: δ 8.08 (1H, s), 7.78-7.75 (1H, d), 7.25-7.22 (1H, m), 7.16-7.15 (2H, m), 6.96-6.93 (1H, d), 4.69 (2H, s), 3.24 (3H, s).
MS: ESI(-ve) 373 (M-1)

Example 43

{2-[2-Chloro-4-(ethylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid

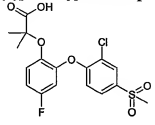


The title compound was prepared by the method of example 42 using the product from example 8 step (i).

1H NMR: DMSO-d6: δ 8.00-7.99 (1H, m), 7.72-7.69 (1H, d), 7.21-7.02 (4H, m), 4.43 (2H, s), 3.40-3.30 (2H, q), 1.12-1.07 (3H, t).
MS: ESI(-ve) 387 (M-1)

Example 44

2-{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}-2-methylpropanoic acid



(i) tert-Butyl 2-(4-fluoro-2-methoxyphenoxy)-2-methylpropanoate

Potassium carbonate (0.97g) was added to a solution of 2-methoxy-4-fluorophenol (1.0g) and tert-butyl-2-bromoisobutyrate (1.31ml) in acetonitrile (20ml) and heated under reflux for 26h. The mixture was diluted with water and extracted with ethyl acetate, the organics were dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with using isohexane:diethylether 3:1, yield 0.83g.
1H NMR: $CDCl_3$: δ 6.94-6.89 (1H, m), 6.64-6.59 (1H, m), 6.55-6.49 (1H, m), 3.79 (3H, s), 1.52-1.41 (15H, 2 x s).

(ii) 2-(4-Fluoro-2-hydroxyphenoxy)-2-methylpropanoic acid

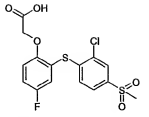
The subtitle compound was prepared by the method of example 28 step (iii) using the product from step (i), yield 0.7g.
MS: ESI(-ve) 213 (M-1)

(iii) 2-{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}-2-methylpropanoic acid

The title compound was prepared by the method of example 1 step (ii) using the product from step (ii), yield 0.065g
1H NMR: DMSO-d6: δ 8.08-8.07 (1H, s), 7.79-7.75 (1H, d), 7.27-7.23 (1H, m), 7.12-7.09 (2H, m), 6.97-6.95 (1H, d), 3.24 (3H, s), 1.23 (6H, s).
MS: ESI(-ve) 401 (M-1)

Example 45

(2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid



(i) 5-Fluoro-2-methoxybenzenesulfonyl chloride

4-Fluoroanisole (10.0g) was carefully added to chlorosulphonic acid (45.81g) at 0°C. The mixture was stirred at RT for 2h, then quenched with ice-water (500ml) and the solid filtered and dried, yield 16.50g.

1H NMR: $CDCl_3$: δ 7.72-7.68 (1H, m), 7.44-7.38 (1H, m) 7.12-7.08 (1H, m), 4.05 (3H, s).

(ii) 5-Fluoro-2-methoxybenzenethiol

The subtitle compound was prepared by the method of example 1 step (i) using the product from step (i), yield 1.7g.

MS: ESI (-ve) 157 (M-1)

(iii) 3-Chloro-4-[(5-fluoro-2-methoxyphenyl)thio]phenyl methyl sulfone

The subtitle compound was prepared by the method of example 1 step (ii) using the product from step (ii) and the product from example 7 step (ii), yield 0.8g.

1H NMR: $CDCl_3$: δ 7.91-7.90 (1H, s), 7.59-7.56 (1H, d) 7.26-7.17 (2H, m), 7.00-6.96 (1H, m), 6.82-6.79 (1H, d), 3.80 (3H, s), 3.03 (3H, s).

(iv) 2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenol

The subtitle compound was prepared by the method of example 1 step (iii) using the product from step (iii), yield 0.6g.

MS: ESI (-ve) 331 (M-1)

(v) (2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid

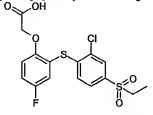
Sodium hydride (60% disp. oil, 0.024g) was added to the product from step (iv) (0.20g) in dry DMF (10ml) and stirred at RT for 30min before adding methyl-bromoacetate (0.060ml). The solution was stirred at RT for 2h, diluted with water and extracted with diethylether. The organics were dried and evaporated under reduced pressure to give an oil. The oil was dissolved in THF (20ml) and water (10ml) then sodium hydroxide (0.037g) was added and stirred at RT overnight. The mixture was acidified with 2M HCl, extracted with ethyl acetate, the organics dried and evaporated under reduced pressure. The residue was purified by reverse phase HPLC. Yield 0.045g

1H NMR: DMSO-d6: δ 8.00-7.99 (1H, s), 7.70-7.66 (1H, d), 7.45-7.37 (2H, m), 7.18-7.14 (1H, m), 7.02-6.99 (1H, m), 4.77(2H, s), 3.24 (3H, s).

MS: ESI(-ve) 389 (M-1)

Example 46

(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid



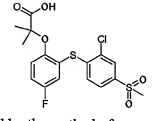
The title compound was prepared by the method of example 45 using the product from example 8 step (i), yield 0.029g.

1H NMR: DMSO-d6: δ 7.92 (1H, s), 7.64-7.61 (1H, d), 7.44-7.34 (2H, m), 7.10-7.06 (2H, m), 4.55(2H, s), 3.41-3.28 (2H, q), 1.11-1.06 (3H, t).

MS: ESI(-ve) 403 (M-1)

Example 47

2-(2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)-2-methylpropanoic acid



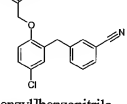
The title compound was prepared by the method of example 29 step (ii) using the product from example 45 step (iv), yield 0.05g.

1H NMR: DMSO-d6: δ 7.98-7.97 (1H, s), 7.70-7.67 (1H, d), 7.32-7.20 (2H, m), 7.07-7.02 (2H, m), 3.24 (3H, s), 1.21 (6H, s).

MS: ESI(-ve) 417 (M-1)

Example 48

[4-Chloro-2-(3-cyanobenzyl)phenoxy]acetic acid



(i) 3-[2-(Benzyloxy)-5-chlorobenzyl]benzonitrile

A mixture of 2-benzyloxy-5-chlorophenylboronic acid (2.1g), 3-cyanobenzyl bromide (1.57g), sodium carbonate (1.7g) and tetrakis(triphenylphosphine)palladium (0) (0.46g) in

ethylene glycol dimethyl ether (30ml) was heated at 80°C for 5h. The mixture was cooled, partitioned between water/diethylether, the organics separated, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 5% ethylacetate/isohexane, yield 0.53g.

^{1}H NMR DMSO-d6: δ 7.68-7.24 (11H, m) ; 7.08 (1H, d) ; 5.10 (2H, s) ; 3.97 (2H, s)

(ii) [4-Chloro-2-(3-cyanobenzyl)phenoxy]acetic acid

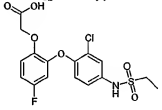
The title compound was prepared by the method of example 1 steps (iii-v) using the product from step (i), yield 0.175g.

^{1}H NMR DMSO-d6: δ 7.81 (1H, s) ; 7.68-7.63 (2H, m) ; 7.47 (1H, t) ; 7.34 (1H, d) ; 7.24 (1H, dd) ; 6.93 (1H, d) ; 4.74 (2H, s) ; 3.99 (2H, s)

MS: APCI(-ve) 300/302 (M-1)

Example 49

(2-{2-Chloro-4-[(ethylsulfonyl)amino]phenoxy}-4-fluorophenoxy)acetic acid



(i) 2-Chloro-1-(5-fluoro-2-methoxyphenoxy)-4-nitrobenzene

Sodium hydride (60% disp. oil, 0.281g) was added to a solution of 5-fluoro-2-methoxyphenol (1.0g) in DMF (20ml) and stirred at RT for 30min. 2-Chloro-1-fluoro-4-nitrobenzene (1.23g) was added and the mixture stirred at RT for 16h then diluted with water and extracted with diethylether. The organics were dried and evaporated under reduced pressure, yield 1.95g.

MS: ESI(-ve) 296 (M-1)

(ii) 3-Chloro-4-(5-fluoro-2-methoxyphenoxy)aniline

Iron powder (2.0g) was added to a solution of the product from step (i) (1.95g) in acetic acid (40ml) and the mixture stirred at RT overnight. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was partitioned between aqueous sodium hydrogencarbonate soln and ethylacetate, the organics dried and evaporated under reduced pressure.

MS: ESI (+ve) 268 (M+1)

(iii) 2-(4-Amino-2-chlorophenoxy)-4-fluorophenol

The subtitle compound was prepared by the method of example 1 step (iii) using the product from step (ii), yield 0.75g.

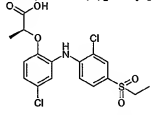
MS: ESI (-ve) 252 (M-1)

(iv) tert-Butyl [2-(4-amino-2-chlorophenoxy)-4-fluorophenoxy]acetate
The subtitle compound was prepared by the method of example 1 step (iv) using the product from step (iii), yield 0.38g.
^{1}H NMR $CDCl_3$: δ 6.96-6.33 (6H, m) ; 4.62 (2H, s) ; 3.68 (2H, s) ; 1.47 (9H, s)

(v) (2-{2-Chloro-4-[(ethylsulfonyl)amino]phenoxy}-4-fluorophenoxy)acetic acid
Ethane sulphonyl chloride (0.05ml) was added to a solution of the product from step (iv) (0.19g) in pyridine (10ml) and stirred at RT for 2h. The solvent was evaporated under reduced pressure and the residue dissolved in DCM (10ml) and trifluoroacetic acid (10ml). After stirring at RT for 2h the solvent was removed and the residue purified by RPHPLC, yield 0.062g.
^{1}H NMR DMSO-d6: δ 7.36-6.74 (6H, m) ; 4.59 (2H, s) ; 3.16-3.08 (2H, q) ; 1.22-1.18 (3H, t)
MS: ESI (-ve) 402 (M-1)

Example 50

(2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)propanoic acid

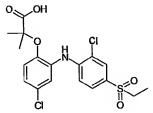


(i) 4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenol
The subtitle compound was prepared by the method of example 1 step (ii) using the product from example 8 step (i) (1.0g) and 5-chloro-2-benzoxazolone (0.85g), yield 0.55g.
MS: ESI (-ve) 345 (M-1)

(ii) (2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)propanoic acid
The title compound was prepared by the method of example 16 using the product from step (i) (0.24g), yield 0.04g.
^{1}H NMR DMSO-d6: δ 8.84 (1H, bs) ; 7.80 (1H, s) ; 7.58 (1H, s) ; 7.34 (1H, s) ; 7.17-7.06 (3H, m) ; 4.60 (1H, q) ; 3.24 (2H, q) ; 1.36 (3H, d) ; 1.09 (3H, t)
MS: ESI (-ve) 416 (M-1)

Example 51

2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)-2-methylpropanoic acid



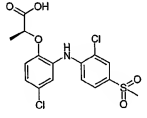
The title compound was prepared by the method of example 29 step (ii) using the product from example 50 step (i), yield 0.16g.

^{1}H NMR DMSO-d6: δ 8.15 (1H, bs) ; 7.83 (1H, s) ; 7.60 (1H, d) ; 7.36 (1H, s) ; 7.13 (1H, d) ; 7.01-6.94 (2H, m) ; 3.27 (2H, q) ; 1.38 (6H, s) ; 1.08 (3H, t)

MS: ESI (-ve) 430 (M-1)

Example 52

(2S)-2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)propanoic acid



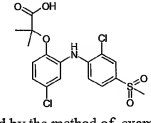
The title compound was prepared by the method of example 50 using the product from example 7 step (ii), yield 0.075g.

^{1}H NMR DMSO-d6: δ 7.94 (1H, s) ; 7.88 (1H, s) ; 7.64 (1H, d) ; 7.37-7.32 (1H, m) ; 7.20-7.06 (3H, m) ; 4.89 (1H, q) ; 3.18 (3H, s) ; 1.38 (3H, d)

MS: ESI (-ve) 402 (M-1)

Example 53

2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)-2-methylpropanoic acid

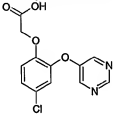


The title compound was prepared by the method of example 50 step (i) and example 29 step (ii), yield 0.05g.

^{1}H NMR DMSO-d6: δ 7.86 (1H, s) ; 7.64 (1H, d) ; 7.28-7.22 (1H, m) ; 7.10-7.06 (2H, m) ; 7.02 (1H, d) ; 3.17 (3H, s) ; 1.39 (6H, s)
MS: ESI (-ve) 416 (M-1)

Example 54

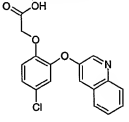
[4-Chloro-2-(pyrimidin-5-yloxy)phenoxy]acetic acid



A mixture of the product from example 5 step (ii) (0.2g), 5-bromopyrimidine (0.308g), tetramethylheptane-3,5-dione (0.046g), cesium carbonate (0.65g) and cuprous chloride (0.045g) in NMP (2ml) was heated at 130°C overnight then at 150°C. The mixture was filtered, the filtrate washed with diethylether, acidified to pH 4 with 2M hydrochloric acid and extracted with ethylacetate. The ethylacetate layer was washed with water, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with ethylacetate/acetic acid. Yield 0.007g
^{1}H NMR DMSO-d6: δ 8.92 (1H, s) ; 8.52 (2H, s) ; 7.42 (1H, s) ; 7.33 (1H, dd) ; 7.13 (1H, d) ; 4.74 (2H, s)
MS: ESI (-ve) 279 (M-1)

Example 55

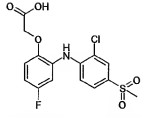
[4-Chloro-2-(quinolin-3-yloxy)phenoxy]acetic acid



The title compound was prepared by the method of example 54, yield 0.035g.
^{1}H NMR DMSO-d6: δ 8.00 (1H, d) ; 7.84 (1H, d) ; 7.67-7.63 (2H, m) ; 7.54 (1H, t) ; 7.38 (1H, d) ; 7.32 (1H, dd) ; 7.17 (1H, d) ; 4.74 (2H, s)
MS: ESI (-ve) 328 (M-1)

Example 56

(2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid



(i) 2-Chloro-N-(5-fluoro-2-methoxyphenyl)-4-(methylsulfonyl)aniline

A mixture of 2-bromo-4-fluoroanisole (6.0g), 2-chloro-4-methylsulphonylaniline (9.0g), cesium carbonate (14.7g), palladium acetate (0.33g) and 2-(dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl (0.54g) in dioxane (60ml) was heated at 100°C for 20h. The mixture was cooled, and partitioned between ethylacetate/water. The organics were separated, washed with brine, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 25% ethylacetate/isohexane. Yield 3.2g

MS: ESI (+ve) 330 (M+1)

(ii) 2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenol

The subtitle compound was prepared by the method of example 1 step (iii) using the product from step (i), yield 2.2g.

MS: ESI (+ve) 316 (M+1)

(iii) (2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid

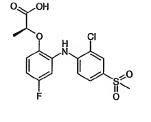
Sodium tert-butoxide (0.073g) was added to a solution of the product from step (ii) (0.2g) in THF (10ml) and stirred at RT for 5min. Ethyl bromoacetate (0.078ml) was added, the mixture stirred for 1h before adding 2M sodium hydroxide solution (2ml). After 3h, 2M hydrochloric acid was added and the mixture extracted with ethyl acetate. The organics were washed with brine, dried and evaporated under reduced pressure. The residue was purified by RPHPLC, yield 0.11g.

^{1}H NMR DMSO-d6: δ 13.14 (s, 1H), 7.97 (s, 1H), 7.89 (s, 1H), 7.64 (d, 1H), 7.20 (d, 1H), 7.12 (m, 2H), 6.98 (m, 1H), 4.75 (s, 2H), 3.18 (s, 3H)

MS: ESI (-ve) 372 (M-1)

Example 57

(2S)-2-(2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)propanoic acid



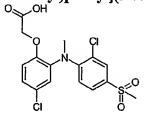
Diisopropyl azodicarboxylate (0.14ml) was added to a stirred solution of the product from example 56 step (ii) (0.2g), triphenylphosphine (0.18g), R-methyl lactate (0.1g) in THF (10ml). After 20h, aqueous 1M sodium hydroxide solution (2ml) was added and stirred for 4h. The mixture was diluted with water (30ml) then partitioned between ethyl acetate/2M hydrochloric acid. The organics were separated, washed with brine, dried and evaporated under reduced pressure. The residue was purified by RPHPLC, yield 0.094g.

^{1}H NMR DMSO-d6: δ 13.23 (s, 1H), 7.99 (s, 1H), 7.90 (s, 1H), 7.66 (d, 1H), 7.22 (m, 2H), 7.12 (m, 1H), 6.96 (m, 1H), 4.86 (q, 1H), 3.18 (s, 3H), 1.43 (d, 3H)

MS: ESI (-ve) 386 (M-1)

Example 58

{4-Chloro-2-[[2-chloro-4-(methylsulfonyl)phenyl](methyl)amino]phenoxy}acetic acid



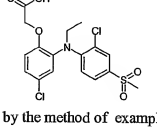
Sodium hydride (60% disp. oil, 0.11g) was added to a solution of the product from example 31(0.5g) in DMF (5ml) and stirred at RT for 10min. Methyl iodide (1ml) was added, stirred for 5h then methanol (1ml) added followed by 1M sodium hydroxide solution (3ml). After stirring for a further 20h the mixture was acidified with 2M hydrochloric acid and extracted with ethyl acetate. The organics were washed with brine, dried and evaporated under reduced pressure. The residue was purified by RPHPLC, yield 0.21g.

^{1}H NMR DMSO-d6: δ 13.01 (s, 1H), 7.82 (d, 1H), 7.81 (s, 1H), 7.43 (d, 1H), 7.15 (d, 1H), 7.00 (d, 1H), 6.84 (s, 1H), 4.69 (s, 2H), 3.27 (s, 3H), 3.23 (s, 3H)

MS: ESI (-ve) 402 (M-1)

Example 59

{4-Chloro-2-[[2-chloro-4-(methylsulfonyl)phenyl](ethyl)amino]phenoxy}acetic acid

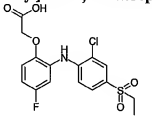


The title compound was prepared by the method of example 58 using iodoethane, yield 0.017g.

^{1}H NMR DMSO-d6: δ 7.79 (s, 1H), 7.78 (d, 1H), 7.44 (d, 1H), 7.13 (d, 1H), 6.99 (d, 1H), 6.82 (s, 1H), 4.63 (s, 2H), 3.80 (q, 2H), 3.23 (s, 3H), 1.13 (t, 3H)
MS: ESI (-ve) 416 (M-1)

Example 60

(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid



(i) 5-Fluoro-1,3-benzoxazol-2(3H)-one

A solution of 2-amino-4-fluorophenol (4.0g), carbonyldiimidazole (1.7g) in DCM (100ml) and acetonitrile (30ml) was stirred at RT for 5h. The solvent was removed under reduced pressure and the residue purified by chromatography on silica eluting with 30% ethylacetate/isohexane, yield 4.0g.
MS: ESI (+ve) 154 (M+1)

(ii) 2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenol

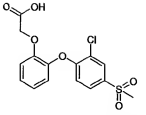
A mixture of the product from step (i) (1.38g), the product from example 8 step (i) (2.0g) and potassium carbonate (3.7g) in NMP (20ml) was heated in a CEM microwave (100°C/50 watts) for 15min. Methanol (30ml) followed by 1M sodium hydroxide solution were added and the reaction stirred at RT for 3h. The mixture was acidified with 2M hydrochloric acid, extracted with ethyl acetate, the organics washed with water, brine, dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 25% ethylacetate/isohexane, yield 2.0g.
MS: ESI (+ve) 330 (M+1)

(iii) (2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid

The title compound was prepared by the method of example 56 step (iii) using the product from step (ii), yield 0.35g.
^{1}H NMR DMSO-d6: δ 13.14 (s, 1H), 7.99 (s, 1H), 7.82 (s, 1H), 7.59 (d, 1H), 7.22 (d, 1H), 7.12 (s, 1H), 7.11 (d, 1H), 6.99 (m, 1H), 4.74 (s, 2H), 3.25 (q, 2H), 1.10 (t, 3H)
MS: ESI (-ve) 386 (M-1)

Example 61

{2-[2-Chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid



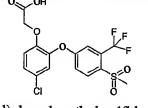
Sodium hydride (60% disp. oil, 0.24g) was added to a solution of (2-hydroxyphenoxy) acetic acid (0.5g) in DMF (20ml) and stirred at 40°C for 30min. The product from example 7 step (ii) (0.62g) was added, then the mixture heated at 75°C for 30h. 2M Sodium hydroxide solution was added and extracted with ethylacetate. The aqueous layer was acidified with 2M hydrochloric acid and extracted with ethyl acetate. The organics were dried, evaporated under reduced pressure and the residue purified by RPHPLC, yield 0.21g.

^{1}H NMR DMSO-d6: δ 8.05-6.93 (7H, m) ; 4.47 (2H, s) ; 3.23 (3H, s)

MS: APCI (-ve) 355 (M-1)

Example 62

{4-Chloro-2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]phenoxy}acetic acid



(i) 4-Bromo-2-(trifluoromethyl)phenyl methyl sulfide

A mixture of sodium thiomethoxide (0.317g) and 5-bromo-2-fluorobenzotrifluoride (1.0g) in DMF (4ml) was heated at 50°C for 1h then poured into water and extracted with isohexane. The organics were washed with brine, dried and evaporated under reduced pressure. Yield 0.762g

^{1}H NMR DMSO-d6: δ 7.74 (1H, d) ; 7.59 (1H, dd) ; 7.22 (1H, d) ; 2.51 (3H, s)

(ii) 4-Bromo-2-(trifluoromethyl)phenyl methyl sulfone

The subtitle compound was prepared by the method of example 2 step (ii) using the product from step (i), yield 0.8g.

(iii) Methyl {4-chloro-2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]phenoxy} acetate

A mixture of sodium tert-butoxide (0.96g), the product from example 5 step (ii) (0.4g) in DMSO (10ml) was stirred at RT for 1h, then the product from step (ii) (0.66g) added. The mixture was heated at 120°C for 6h, cooled and partitioned between ethyl acetate/2M hydrochloric acid. The organics were separated, washed with water, dried and evaporated

under reduced pressure. The residue was esterified using trimethyldiazomethane in DCM/methanol, yield 0.205g.

^{1}H NMR $CDCl_3$: δ 8.22 (1H, d) ; 7.47 (1H, d) ; 7.27-7.13 (3H, m) ; 6.86 (1H, d) ; 4.61 (2H, s) ; 3.74 (3H, s) ; 3.17 (3H, s) ;

(iv) {4-Chloro-2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]phenoxy}acetic acid

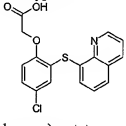
1M Sodium hydroxide solution (0.5m) was added to a solution of the product from step (iii) (0.197g) in methanol (1ml) and tetrahydrofuran (3ml) and stirred at RT for 16h. The solvent was evaporated under reduced pressure and the residue partitioned between DCM/2M hydrochloric acid. The organics were dried, evaporated under reduced pressure and the residue recrystallised from DCM-isohexane, yield 0.108g.

^{1}H NMR DMSO-d6: δ 13.10 (1H, s) ; 8.16 (1H, d) ; 7.51 (1H, d) ; 7.46 (1H, d) ; 7.38 (1H, dd) ; 7.33 (1H, dd) ; 7.18 (1H, d) ; 4.75 (2H, s) ; 3.24 (3H, s)

MS: APCI (-ve) 423 (M-1)

Example 63

[4-Chloro-2-(quinolin-8-ylthio)phenoxy]acetic acid



(i) tert-Butyl (4-chloro-2-iodophenoxy)acetate

The subtitle compound was prepared by the method of example 1 step (iv) using 4-chloro-2-iodo-phenol (4.75g), yield 6.88g.

^{1}H NMR $CDCl_3$: δ 7.77 (1H, d) ; 7.24 (1H, dd) ; 6.61 (1H, d) ; 4.55 (2H, s) ; 1.48 (9H, s)

(ii) [4-Chloro-2-(quinolin-8-ylthio)phenoxy]acetic acid

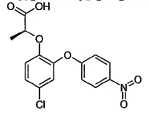
A mixture of the product from step (i) (0.262g), 8-quinolinethiol hydrochloride (0.141g), copper (I) iodide (7mg), potassium carbonate (0.295g) and ethylene glycol (0.08ml) in iso-propanol (3ml) was heated at 80°C for 48h. The mixture was partitioned between DCM/2M hydrochloric acid, the organics dried, evaporated under reduced pressure and the residue purified by chromatography on silica eluting with DCM:methanol:acetic acid (90:9:1). The residue was triturated with diethylether/methanol, filtered and dried, yield 0.101g.

^{1}H NMR DMSO-d6: δ 13.00 (1H, bs) ; 8.95 (1H, d) ; 8.42 (1H, d) ; 7.81 (1H, d) ; 7.63 (1H, dd) ; 7.57-7.37 (3H, m) ; 7.08 (2H, d) ; 4.79 (2H, s)

MS: APCI (-ve) 344/6 (M-1)

Example 64

(2*S*)-2-[4-Chloro-2-(4-nitrophenoxy)phenoxy]-propanoic acid



(i) Methyl (2S)-2-(4-chloro-2-formylphenoxy)propanoate

The subtitle compound was prepared by the method of example 1 step (ii) using 5-chloro-2-hydroxybenbaldehyde and methyl (2R)-2-(4-toluenesulphonyl)lactate

^{1}H NMR $CDCl_3$: δ 10.50 (1H, s) ; 7.81 (1H, d) ; 7.44 (1H, dd) ; 6.79 (1H, d) ; 4.87 (1H, q) ; 3.77 (3H, s) ; 1.70 (3H, d)

(ii) (2S)-2-(4-Chloro-2-hydroxyphenoxy)propanoic acid

The subtitle compound was prepared by the method of example 1 step (ii) and example 26 step (iv) using the product from step (i).

MS: APCI (-ve) 215/7 (M-1)

(iii) (2*S*)-2-[4-Chloro-2-(4-nitrophenoxy)phenoxy]-propanoic acid

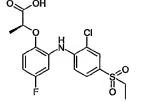
To a solution of (2*S*)-2-(4-chloro-2-hydroxyphenoxy)-propanoic acid (0.216 g) and 1-fluoro-4-nitro-benzene (0.127 g) in NMP (3 ml) was added potassium carbonate (0.276 g) and the reaction heated at 90°C for 2h. After cooling to RT, water and diethylether were added. The aqueous layer was separated and extracted again with diethylether. The aqueous layer was isolated, acidified to pH 2 and extracted with diethylether. This later extract was dried and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 30-50% ethylactate / isohexane + 1%AcOH, yield 0.2g

^{1}H NMR DMSO-d6: δ 8.22 (2H, d), 7.40 (1H, d), 7.34 (1H, dd), 7.09 (3H, m), 4.85 (1H, q), 1.26 (3H, d).

MS: APCI (-ve) 336

Example 65

(2S)-2-(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)propanoic acid



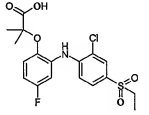
The title compound was prepared by the method of example 57 using the product from example 60 step (ii).

^{1}H NMR DMSO-d6: δ 13.22 (s, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.61 (d, 1H), 7.24 (d, 1H), 7.18 (d, 1H), 7.12 (m, 1H), 6.97 (m, 1H), 4.85 (q, 1H), 3.26 (q, 2H), 1.42 (d, 3H), 1.10 (t, 3H)

MS: APCI (-ve) 400

Example 66

2-(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)-2-methylpropanoic acid, sodium salt



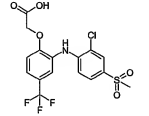
The title compound was prepared by the method of example 29 step (ii) using the product from example 60 step (ii).

^{1}H NMR DMSO-d6: δ 10.67 (s, 1H), 7.77 (s, 1H), 7.56 (d, 1H), 7.22 (d, 1H), 7.04 (m, 2H), 6.75 (m, 1H), 3.24 (q, 2H), 1.38 (s, 6H), 1.10 (t, 3H)

MS: APCI (-ve) 414

Example 67

[2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid



(i) 2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenol

The subtitle compound was prepared by the method of example 60 step (ii) using 5-(trifluoromethyl)-1,3-benzoxazol-2(3H)-one and the product from example 7 step (ii).

MS: ESI (+ve) 366 (M+1)

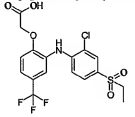
(ii) [2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy] acetic acid

The title compound was prepared by the method of example 56 step (iii) using the product from step (i).

^{1}H NMR DMSO-d6: δ 8.50 (s, 1H), 7.86 (s, 1H), 7.59 (m, 2H), 7.49 (d, 1H), 7.19 (d, 1H), 7.02 (d, 1H), 4.60 (s, 2H), 3.17 (s, 3H)
MS: APCI (-ve) 422 (M-1)

Example 68

[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid



(i) 2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenol
The subtitle compound was prepared by the method of example 60 step (ii) using 5-(trifluoromethyl)-1,3-benzoxazol-2(3H)-one and the product from example 8 step (i).
MS: ESI (+ve) 380 (M+1)

(ii) [2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid
The title compound was prepared by the method of example 56 step (iii) using the product from step (i).
^{1}H NMR DMSO-d6: δ 13.18 (s, 1H), 8.09 (s, 1H), 7.81 (s, 1H), 7.63 (s, 1H), 7.55 (m, 2H), 7.23 (d, 1H), 6.87 (d, 1H), 4.85 (s, 2H), 3.24 (q, 2H), 1.10 (t, 3H)
MS: APCI (-ve) 436 (M-1)

Pharmacological Data

Ligand Binding Assay

[^{3}H]PGD_2 was purchased from Perkin Elmer Life Sciences with a specific activity of 100-210Ci/mmol. All other chemicals were of analytical grade.

HEK cells expressing rhCRTh2 / Gα16 were routinely maintained in DMEM containing 10% Foetal Bovine Serum (HyClone), 1mg/ml geneticin, 2mM L-glutamine and 1% non-essential amino acids. For the preparation of membranes, the adherent transfected HEKcells were grown to confluence in two layer tissue culture factories (Fisher, catalogue number TKT-170-070E). Maximal levels of receptor expression were induced by addition of 500mM sodium butyrate for the last 18 hours of culture. The adherent cells were washed once with phosphate buffered saline (PBS, 50ml per cell factory) and detached by the addition of 50ml per cell factory of ice-cold membrane homogenisation buffer [20mM

HEPES (pH 7.4), 0.1mM dithiothreitol, 1mM EDTA, 0.1mM phenyl methyl sulphonyl fluoride and 100μg/ml bacitracin]. Cells were pelleted by centrifugation at 220xg for 10 minutes at 4°C, re-suspended in half the original volume of fresh membrane homogenisation buffer and disrupted using a Polytron homogeniser for 2 x 20 second bursts keeping the tube in ice at all times. Unbroken cells were removed by centrifugation at 220xg for 10 minutes at 4°C and the membrane fraction pelleted by centrifugation at 90000xg for 30 minutes at 4°C. The final pellet was re-suspended in 4 ml of membrane homogenisation buffer per cell factory used and the protein content determined. Membranes were stored at -80°C in suitable aliquots.

All assays were performed in Corning clear bottomed, white 96-well NBS plates (Fisher). Prior to assay, the HEK cells membranes containing CRTh2 were coated onto SPA PVT WGA beads (Amersham). For coating membranes were incubated with beads at typically 25μg membrane protein per mg beads at 4°C with constant agitation overnight. (The optimum coating concentrations were determined for each batch of membranes) The beads were pelleted by centrifugation (800xg for 7minutes at 4°C), washed once with assay buffer (50mM HEPES pH 7.4 containing 5mM magnesium chloride) and finally re-suspended in assay buffer at a bead concentration of 10mg/ml.

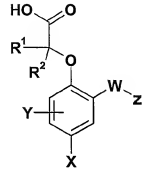
Each assay contained 20μl of 6.25nM [^{3}H]PGD_2, 20μl membrane saturated SPA beads both in assay buffer and 10μl of compound solution or 13,14-dihydro-15-keto prostaglandin D_2 (DK-PGD_2, for determination of non-specific binding, Cayman chemical company). Compounds and DK-PGD_2 were dissolved in DMSO and diluted in the same solvent to 100x the required final concentration. Assay buffer was added to give a final concentration of 10% DMSO (compounds were now at 10x the required final concentration) and this was the solution added to the assay plate. The assay plate was incubated at room temperature for 2 hours and counted on a Wallac Microbeta liquid scintillation counter (1 minute per well).

Compounds of formula (I) have an IC_{50} value of less than (<) 10μM.

Specifically, example 4 has a $pIC_{50} = 8.0$, example 5 has a $pIC_{50} = 8.0$ and example 43 has a $pIC_{50} = 9.0$.

Claims

1. A method of treatment of diseases or conditions in which modulation of CRTh2 receptor activity is beneficial, which comprises administering to a patient a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

in which:

W is O, $S(O)_n$ (where n is 0, 1 or 2), NR^{15}, CR^1OR^2 or CR^1R^2;

X is hydrogen, halogen, cyano, nitro, $S(O)_n R^6$, OR^{12} or C_{1-6}alkyl which may be substituted by one or more halogen atoms;

Y is hydrogen, halogen, CN, nitro, SO_2R^3, OR^4, SR^4, SOR^3, $SO_2NR^4R^5$, $CONR^4R^5$, NR^4R^5, $NR^6SO_2R^3$, $NR^6CO_2R^6$, NR^6COR^3, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, OR^6 and NR^6R^7, $S(O)_nR^6$ where n is 0, 1 or 2;

Z is aryl or heteroaryl, optionally substituted by one or more substituents independently selected from from hydrogen, halogen, CN, OH, SH, nitro, CO_2R^6, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NR^6CO_2R^6$, $NHCOR^9$, NR^9COR^9, aryl, heteroaryl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter four groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6, NR^6R^7, $S(O)_nR^6$ (where n is 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$.

R^1 and R^2 independently represent a hydrogen atom, halogen, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl or a C_{1-6}alkyl group, the latter four groups being optionally

substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, NR^6R^7, OR^6, $S(O)_nR^6$ (where n is 0, 1 or 2);

or

R^1 and R^2 together can form a 3-8 membered ring optionally containing one or more atoms selected from O, S, NR^6 and itself optionally substituted by one or more C_1-C_3 alkyl or halogen;

R^3 represents C_3-C_7 cycloalkyl or C_{1-6}alkyl either of which may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0,1 or 2), $CONR^6R^7$, NR^6COR^7,$SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^4 and R^5 independently represent hydrogen, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0,1 or 2), $CONR^6R^7$, NR^6COR^7,$SO_2NR^6R^7$ and $NR^6SO_2R^7$;

or

R^4 and R^5 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_n$ (where n = 0,1 or 2), NR^8, and itself optionally substituted by halogen or C_1-$_3$ alkyl;

R^6 and R^7 independently represents a hydrogen atom or C_1-C_6 alkyl;

R^8 is hydrogen, C_1-$_4$ alkyl, -COC_1-C_4 alkyl, CO_2C_1-C_4alkyl, SO_2R^6 or $CONR^5C_1$-C_4alkyl;

R^9 represents aryl, heteroaryl, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups may be optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, aryl, heteroaryl OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

R^{10} and R^{11} independently represent aryl or heteroaryl, hydrogen, C_3-C_7 cycloalkyl or C_{1-6}alkyl, the latter two groups being optionally substituted by one or more substituents independently selected from halogen, C_3-C_7 cycloalkyl, aryl, heteroaryl, OR^6 and NR^6R^7, $S(O)_nR^6$ (where n = 0, 1 or 2), $CONR^6R^7$, NR^6COR^7, $SO_2NR^6R^7$ and $NR^6SO_2R^7$;

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, $S(O)_n$ (where n = 0, 1 or 2), NR^8, and itself optionally substituted by halogen or C_1-C_3 alkyl;

R^{12} represents a hydrogen atom or C_{1-6}alkyl which may be substituted by one or more halogen atoms, and

R^{15} represents a hydrogen atom, C_1-C_6 alkyl, SO_2R^6 or COR^6.

2. A method according to claim 1 in which W is O, $S(O)_n$ (where n is 0, 1 or 2), CR^1R^2 or NR^{15} where R^{15} is hydrogen or methyl.

3. A method according to claim 1 or 2 in which R^1 and R^2 are independently hydrogen or C_{1-3} alkyl.

4. A method according to any one of claims 1 to 3 in which X is halogen, cyano or C_{1-2}alkyl optionally substituted with one or more halogen atoms.

5. A method according to any one of claims 1 to 4 in which Y is hydrogen, halogen or C_{1-6}alkyl.

6. A method according to any one of claims 1 to 5 in which Z is phenyl, pyridyl or pyrimidyl, each optionally substituted by halogen, CN, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NHCOR^9$, NR^9COR^9.

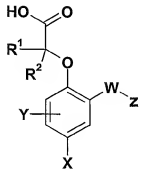
7. A method according to any one of claims 1 to 5 in which Z is phenyl, optionally substituted by halogen, CN, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NHCOR^9$, NR^9COR^9.

8. A method according to any one of claims 1 to 7 where the compound of formula (I) is selected from:
[4-Chloro-2-[[4-(ethylsulfonyl)phenyl]thio]phenoxy]- acetic acid,
[4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]phenoxy]- acetic acid,
[2-[[4-(Ethylsulfonyl)phenyl](hydroxy)methyl]-4-(trifluoromethyl)phenoxy]acetic acid
[2-[4-(Ethylsulfonyl)benzyl]-4-(trifluoromethyl)phenoxy]acetic acid,

[4-Chloro-2-[4-(ethylsulfonyl)phenoxy]phenoxy]- acetic acid,
[4-Chloro-2-[[4-(methylsulfonyl)phenyl]amino]phenoxy]- acetic acid,
(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
{4-Chloro-2-[(5-chloropyridin-2-yl)thio]phenoxy}acetic acid,
{4-Chloro-2-[(2-chloro-4-cyanophenyl)thio]phenoxy}acetic acid,
(4-Chloro-2-{[2-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfinyl}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfonyl}phenoxy)acetic acid,
[4-Chloro-2-({4-[(methylamino)carbonyl]phenyl}thio)phenoxy]acetic acid,
(2S)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2R)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)-2-methylpropanoic acid,
{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}acetic acid,
(2S)-2-{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid,
(2S)-2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid,
(2S)-2-{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}propanoic acid,
{4,5-Dichloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4,5-difluorophenoxy}acetic acid,
2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}-2-methylpropanoic acid,
(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)acetic acid,
(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)acetic acid,
[2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid,
(2S)-2-[2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]propanoic acid,
[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid,
(2S)-2-[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]propanoic acid,
[2-({4-[(Dimethylamino)sulfonyl]phenyl}thio)-4-(trifluoromethyl)phenoxy]acetic acid,
[2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid,
[2-[2-Chloro-4-(ethylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid,
2-[2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]butanoic acid,
[2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]acetic acid,

(2S)-2-[2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]propanoic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid,
{2-[2-Chloro-4-(ethylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid,
2-{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}-2-methylpropanoic acid,
(2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid,
(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid,
2-(2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)-2-methylpropanoic acid,
[4-Chloro-2-(3-cyanobenzyl)phenoxy]acetic acid,
(2-{2-Chloro-4-[(ethylsulfonyl)amino]phenoxy}-4-fluorophenoxy)acetic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)propanoic acid,
2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)-2-methylpropanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)propanoic acid,
2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)-2-methylpropanoic acid,
[4-Chloro-2-(pyrimidin-5-yloxy)phenoxy]acetic acid,
[4-Chloro-2-(quinolin-3-yloxy)phenoxy]acetic acid,
(2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid,
(2S)-2-(2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)propanoic acid,
{4-Chloro-2-[[2-chloro-4-(methylsulfonyl)phenyl](methyl)amino]phenoxy}acetic acid,
{4-Chloro-2-[[2-chloro-4-(methylsulfonyl)phenyl](ethyl)amino]phenoxy}acetic acid,
(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]phenoxy}acetic acid,
[4-Chloro-2-(quinolin-8-ylthio)phenoxy]acetic acid,
(2*S*)-2-[4-Chloro-2-(4-nitrophenoxy)phenoxy]-propanoic acid,
(2S)-2-(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)propanoic acid,
2-(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)-2-methylpropanoic acid,
[2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid,
[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid
and pharmaceutically acceptable salts and solvates thereof.

9. A compound of formula (IA) or pharmaceutically acceptable salts or solvates thereof:



(IA)

in which:

W is O, CH_2, $S(O)_n$ (where n is 0, 1 or 2) or NR^{15} where R^{15} is hydrogen or methyl;

X is halogen or C_{1-6}alkyl which may be substituted by one or more halogen atoms;

Y is hydrogen, halogen or C_{1-6}alkyl;

Z is phenyl pyridyl or pyrimidyl each optionally substituted by one or more substituents independently selected from from halogen, CN, C_{1-3}alkyl optionally substituted with one or more halogen atoms, SO_2R^9, OR^9, SR^9, SOR^9, $SO_2NR^{10}R^{11}$, $CONR^{10}R^{11}$, $NHSO_2R^9$, $NR^9SO_2R^9$, $NHCOR^9$, NR^9COR^9;

R^1 and R^2 independently represent hydrogen or C_{1-6}alkyl;

R^6 and R^7 independently represent hydrogen atom or C_{1-6}alkyl;

R^8 is hydrogen, C_{1-4} alkyl, $-COC_1-C_4$ alkyl, $CO_2C_1-C_4$alkyl, SO_2R^6 or $CONR^6C_1-C_4$alkyl;

R^9 is C_{1-6}alkyl optionally substituted by halogen, and

R^{10} and R^{11} independently represent hydrogen or C_{1-6}alkyl,
provided that:

- the compounds 2-[4-methyl-2-(benzyl)phenoxy]acetic acid, 2-[4-chloro-2-(benzyl)phenoxy]propanopic acid, 2-[4-bromo-2-(4-chlorophenoxy)phenoxy]propanopic acid and 2-[4-chloro-2-(4-chlorophenoxy)phenoxy]propanopic acid are excluded;
- when X is fluoro and W is S, then Z is not 5-fluoro-2-hydroxyphenyl,

- when X is chloro, Y is 3-methyl, R^1 and R^2 are both hydrogen and W is CH_2, then Z is not phenyl.

10. A compound according to claim 9 in which W is O or NH.

11. A compound according to claim 9 in which W is O.

12. A compound according to any one of claims 9 to 11 in which R^1 and R^2 are independently hydrogen or methyl.

13. A compound according to any one of claims 9 to 12 in which X is fluoro or chloro.

14. A compound according to any one of claims 9 to 13 in which Y is hydrogen.

15. A compound according to any one of claims 9 to 14 in which Z is phenyl substituted in the 4-position by a substituent selected from SO_2R^9, $SO_2NR^{10}R^{11}$, $NHSO_2R^9$ or $NR^9SO_2R^9$ where R^9 is methyl or ethyl, and substituted in the 2- or 3-position by a substituent selected from fluoro, chloro or C_{1-3}alkyl itself optionally substituted with one or more halogen atoms.

16. A compound according to claim 9 selected from:
[4-Chloro-2-[[4-(ethylsulfonyl)phenyl]thio]phenoxy]- acetic acid,
[4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]phenoxy]- acetic acid,
[4-Chloro-2-[4-(ethylsulfonyl)phenoxy]phenoxy]- acetic acid,
[4-Chloro-2-[[4-(methylsulfonyl)phenyl]amino]phenoxy]- acetic acid,
(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
{4-Chloro-2-[(5-chloropyridin-2-yl)thio]phenoxy}acetic acid,
{4-Chloro-2-[(2-chloro-4-cyanophenyl)thio]phenoxy}acetic acid,
(4-Chloro-2-{[2-(methylsulfonyl)phenyl]thio}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfinyl}phenoxy)acetic acid,
(4-Chloro-2-{[4-(methylsulfonyl)phenyl]sulfonyl}phenoxy)acetic acid,
[4-Chloro-2-({4-[(methylamino)carbonyl]phenyl}thio)phenoxy]acetic acid,
(2S)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2R)-2-(4-Chloro-2-{[4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)propanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenoxy)propanoic acid,

2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenoxy)-2-methylpropanoic acid,
{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}acetic acid,
(2S)-2-{4-Chloro-2-[4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid,
(2S)-2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}propanoic acid,
(2S)-2-{4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenoxy}propanoic acid,
{4,5-Dichloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4,5-difluorophenoxy}acetic acid,
2-{4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenoxy}-2-methylpropanoic acid,
(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)acetic acid,
(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)acetic acid,
[2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid,
(2S)-2-[2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]propanoic acid,
[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]acetic acid,
(2S)-2-[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenoxy]propanoic acid,
[2-({4-[(Dimethylamino)sulfonyl]phenyl}thio)-4-(trifluoromethyl)phenoxy]acetic acid,
[2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid,
[2-[2-Chloro-4-(ethylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]acetic acid,
2-[2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-(trifluoromethyl)phenoxy]butanoic acid,
[2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]acetic acid,
(2S)-2-[2-{4-[(Dimethylamino)sulfonyl]phenoxy}-4-(trifluoromethyl)phenoxy]propanoic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid,
{2-[2-Chloro-4-(ethylsulfonyl)phenoxy]-4-fluorophenoxy}acetic acid,
2-{2-[2-Chloro-4-(methylsulfonyl)phenoxy]-4-fluorophenoxy}-2-methylpropanoic acid,
(2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid,
(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]thio}-4-fluorophenoxy)acetic acid,
2-(2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenoxy)-2-methylpropanoic acid,
(2-{2-Chloro-4-[(ethylsulfonyl)amino]phenoxy}-4-fluorophenoxy)acetic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)propanoic acid,
2-(4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenoxy)-2-methylpropanoic acid,
(2S)-2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)propanoic acid,

2-(4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]amino}phenoxy)-2-methylpropanoic acid,
[4-Chloro-2-(pyrimidin-5-yloxy)phenoxy]acetic acid,
[4-Chloro-2-(quinolin-3-yloxy)phenoxy]acetic acid,
(2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid,
(2*S*)-2-(2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenoxy)propanoic acid,
{4-Chloro-2-[[2-chloro-4-(methylsulfonyl)phenyl](methyl)amino]phenoxy}acetic acid,
{4-Chloro-2-[[2-chloro-4-(methylsulfonyl)phenyl](ethyl)amino]phenoxy}acetic acid,
(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)acetic acid,
{2-[2-Chloro-4-(methylsulfonyl)phenoxy]phenoxy}acetic acid,
{4-Chloro-2-[4-(methylsulfonyl)-3-(trifluoromethyl)phenoxy]phenoxy}acetic acid,
[4-Chloro-2-(quinolin-8-ylthio)phenoxy]acetic acid,
(2*S*)-2-[4-Chloro-2-(4-nitrophenoxy)phenoxy]-propanoic acid,
(2*S*)-2-(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)propanoic acid,
2-(2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenoxy)-2-methylpropanoic acid,
[2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid,
[2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenoxy]acetic acid,
[2-[4-(Ethylsulfonyl)benzyl]-4-(trifluoromethyl)phenoxy]acetic acid,
[4-Chloro-2-(3-cyanobenzyl)phenoxy]acetic acid,
and pharmaceutically acceptable salts and solvates thereof.

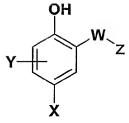
17. A compound of formula (IA) as defined in any one of claims 8 to 16 for use in therapy.

18. A pharmaceutical composition comprising a compound of formula (IA) as defined in any one of claims 9 to 16 or a pharmaceutically acceptable salt thereof in combination with pharmaceutically acceptable carriers or diluents.

19. Use of a compound of formula (I)/(IA), or a pharmaceutically acceptable salt as defined in any one of claims 9 to 16 in the manufacture of a medicament for treating a disease in which modulation of CRTh2 receptor activity is beneficial.

20. Use according to claim 19 wherein the disease is asthma or rhinitis.

21. A process for the preparation of a compound of formula (I) which comprises
(a) reaction of a compound of formula (II):



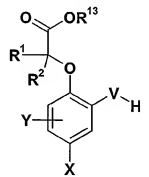
(II)

in which W, X, Y and Z are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (III):

$L\text{-}CR^1R^2CO_2R^{13}$ (III)

where R^1 and R^2 are as defined in formula (I) or are protected derivatives thereof, R^{13} is hydrogen or a C_1-C_{10} alkyl group and L is a leaving group, or

(b) reaction of a compound of formula (V) with a compound of formula (VII):



$Z—L^1$

(V) (VII)

in which X, Y and Z are as defined in formula (I) or are protected derivatives thereof, V is S, NR^6 or O. R^{13} is H or a $C_{1\text{-}10}$alkyl group, and L^1 is iodide, bromide, chloride, fluoride or an activated alcohol,

and optionally thereafter (a) or (b) in any order:

- removing any protecting group
- hydrolysing the ester group R^{13} to the corresponding acid
- oxidation of sulphides to sulphoxides or sulphones
- forming a pharmaceutically acceptable salt.

22. A compound of formula (II) as defined in claim 21.

23. A compound of formula (II) selected from:
4-Chloro-2-[[4-(ethylsulfonyl)-2-methylphenyl]thio]- phenol,
4-Chloro-2-{[2-chloro-4-(methylsulfonyl)phenyl]thio}phenol,
4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]thio}phenol,
4-Chloro-2-[2-chloro-4-(methylsulfonyl)phenoxy]phenol,
4-Chloro-2-[2-chloro-4-(ethylsulfonyl)phenoxy]phenol,
2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-(trifluoromethyl)phenol,
2-{[2-Chloro-4-(methylsulfonyl)phenyl]thio}-4-fluorophenol,
4-Chloro-2-{[2-chloro-4-(ethylsulfonyl)phenyl]amino}phenol,
2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-fluorophenol,
2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-fluorophenol,
2-{[2-Chloro-4-(methylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenol, or
2-{[2-Chloro-4-(ethylsulfonyl)phenyl]amino}-4-(trifluoromethyl)phenol

24. A compound of formula (VII) as defined in claim 21.

25. A compound of formula (VII) selected from:
2-(4-Chloro-2-hydroxyphenoxy)-2-methylpropanoic acid,
(4-Fluoro-2-hydroxyphenoxy)acetic acid,
2-(4-Fluoro-2-hydroxyphenoxy)-2-methylpropanoic acid,
(2S)-2-(4-Chloro-2-hydroxyphenoxy)propanoic acid

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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; Sodertalje, S-SE-151 85 (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BONNERT, Roger, Victor** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **PATEL, Anil** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **THOM, Stephen** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-SE-151 85 Sodertalje (SE).

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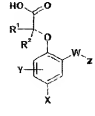
(54) Title: PHENOXIACETIC ACID DERIVATIVES



(I)

(57) Abstract: The invention relates to certain 2-substituted phenoxyacetic acid derivatives of formula (I), in which the variables are as defined in the claims, useful in the treatment of diseases or conditions in which modulation of the CRTh2 receptor is beneficial, such as asthma and rhinitis.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/003551

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IPC 7 C07C205/38 C07C255/54 C07C311/08 C07C311/29 C07C317/22
C07C317/36 C07C323/60 C07C323/65 C07C323/67 C07D213/70
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 031 408 A (KISSEI PHARMACEUTICAL, ET AL.) 23 April 1980 (1980-04-23) page 6, line 20 - line 23; claims 1,15,17,39 ---	1-3,5, 19-25
X	J.H. AMIN, ET AL.: "The Fries reaction: part VI - the rearrangement of aryl p-toluenesulphonates and a convenient method for the synthesis of hydroxy-diarylsulphones" JOURNAL OF SCIENTIFIC & INDUSTRIAL RESEARCH, vol. 13B, 1954, pages 181-183, XP000600360 INDIA page 183, left-hand column, line 3 - line 19 --- -/--	9,12,14, 22

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2005	23/02/2005
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R.C. HUSTON, ET AL.: "Chloro derivatives of benzyl phenols. II. Some monochloro, dichloro and trichloro derivatives of ortho and para benzyl phenols" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 55, no. 11, 1 November 1933 (1933-11-01), pages 4639-4643, XP000616052 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US ISSN: 0002-7863 tabe I, 4th and 10th to 15th entries ---	22
X	GB 1 469 687 A (CIBA-GEIGY) 6 April 1977 (1977-04-06) the whole document ---	22
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X	CH 432 119 A (J.R. GEIGY) 15 March 1967 (1967-03-15) examples ---	22
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/003551

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
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